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The Implication of Frailty on Preoperative Risk Assessment

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Abstract

Purpose of Review—Frailty, a state of decreased homeostatic reserve, is characterized by dysregulation across multiple physiologic and molecular pathways. It is particularly relevant to the perioperative period, during which patients are subject to high levels of stress and inflammation. This review aims to familiarize the anesthesiologist with the most current concepts regarding frailty and its emerging role in preoperative assessment and risk stratification.

Recent findings—Current literature has established frailty as a significant predictor of operative complications, institutionalization, and death among elderly surgical patients. A variety of scoring systems have been proposed to preoperatively identify and assess frail patients, though they differ in their clinical utility and prognostic ability. Additionally, evidence suggests an evolving potential for preoperative intervention and modification of the frailty syndrome.

Summary—The elderly are medically complex and heterogeneous with respect to operative risk. Recent advances in the concept of frailty provide an evidence-based framework to guide the anesthesiologist in the perioperative management, evaluation, and risk stratification of older surgical patients.

Keywords

Frailty; Elderly; Risk Stratification

Introduction

The elderly represent the fastest growing segment of the population [1]. Individuals over the age of 65 comprise a high proportion of health care expenditures [2] and account for over 40% of all surgical procedures [3, 4]. Evidence indicates that this group is heterogeneous with respect to perioperative risk [5, 6]. Age and a simple list of comorbidities (hypertension, diabetes, etc…) often fail to capture the nuances of function and strength in this, population and cannot adequately predict morbidity and mortality [7, 8, 9]. For this

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reason, preoperative risk assessment is especially challenging among seniors, and traditional methods of risk stratification have limited utility [7, 10].

Frailty, a state of decreased physiologic reserve based on a composite of functional and physiologic characteristics, is an important independent predictor of adverse health outcomes [11, 12]. It is particularly relevant to the operative setting, as the prevalence of frailty is higher among seniors who undergo surgery (25.5% to 56.1%) [10, 13**-15*] than their community-dwelling counterparts (6.9%) [12]. Emerging research has established frailty as a strong predictor of operative morbidity and mortality in the elderly [10, 16, 17]. Frailty markers represent a promising method of assessment with the potential to guide physicians in clinical decision-making and risk factor modification [18, 19].

In this article, we will familiarize the anesthesiologist with the most current concepts regarding frailty, and its emerging role in perioperative assessment and risk stratification. We will also review the proposed pathophysiology, assess current methodological issues, and discuss the long-term significance of frailty. In addition, we will discuss various tools available to assess frailty and their relative advantages and disadvantages.

Significance of Frailty in the Perioperative Period

Increasingly, the term “frailty” is used in medical and surgical literature to describe a multidimensional state of weakness, vulnerability and decreased physiologic reserve [19, 20]. Distinct from medical comorbidity and functional disability [12], evidence suggests that frailty more accurately predicts hospitalization, institutionalization, and mortality among elderly outpatients [11, 20]. Frailty is especially important in the perioperative period, during which patients are subject to high levels of physiologic stress and inflammation [19]. One landmark study by Makary et al. demonstrated that frailty was associated with a significantly increased risk of postoperative complication (odds ratio [OR]=2.54) and institutionalization (OR=20.48) [10]. Recent literature has replicated these findings in a variety of surgical settings, including cardiac [21*], thoracic [22*], orthopedic [23*], general [13**, 15*, 24*], otolaryngology [25*], urology, and surgical oncology [14*, 26*].

Assessment Tools

The ability to accurately assess and quantify frailty is essential to patient care, health policy, and the development of evidence-based interventions [27**]. A variety of scoring systems and markers have been proposed to quantify frailty (Table 1). However, a universally accepted definition or standardized measure is lacking [19, 37]. While each of these scales aptly identifies individuals at high risk of adverse outcomes, they capture different sub-populations and differ in their prognostic ability [27**, 38].

Recently, two predominant models of frailty, the frailty phenotype described by Fried et al. [12] and the frailty index (FI) by Mitnitski et al. [28], have emerged. Other theoretical and functional definitions exist on a spectrum between these two approaches [16, 27**]. The frailty phenotype views frailty as a complex biological syndrome, operationalized by functional measures of physical ability, endurance, weakness, slowness, and sarcopenia or weight loss. However, concerns have been raised about the implementation and practicality

of performance-based testing in a fast-paced outpatient setting [27**]. Such measures can be time-consuming, and may require additional training or subspecialty evaluation. Subsequently, the Survey of Health Aging and Retirement in Europe (SHARE) has adapted the frailty phenotype for clinical use. The SHARE Frailty Instrument employs a patient survey and one performance-based measure (handgrip strength) to assess the five domains outlined by Fried [39]. However this methodology has yet to be validated in the perioperative setting.

In contrast, the FI represents a multidimensional risk state measured by the quantity of "deficits" an individual has accumulated. It incorporates 30 to 70 dichotomized deficits including comorbidities, activities of daily living (ADL), and signs from physical and neurological examination [28, 29]. Of note, the FI is a continuous measure, and is thus capable of reflecting dynamic changes in the frailty state. While this scale can be cumbersome, it is readily converted for clinical use as part of an electronic medical record [38]. Such methodology is also easily translated for use in retrospective research. Emerging surgical literature has adopted an 11-item simplified version of the FI, the modified frailty index (mFI), to quantify frailty and risk stratify elderly surgical patients [22*, 23*, 25*, 29, 30**, 32*, 33*].

In addition to the frailty models described above, current efforts to characterize frailty emphasize the use of single surrogate measures, such as gait speed [16, 34, 40*] and grip strength [41]. Recent literature has demonstrated that slower walking speeds, as quantified by the timed up-and-go test, significantly predict postoperative morbidity and mortality (area under the curve [AUC]=0.775) [35**]. Moreover, a history of one or more falls in the six months prior to surgery is strongly associated with operative complications (OR=10.4) [36**]. Of note, these approaches require minimal training and can be administered in less than one minute [35**]. Similarly, a number of novel biomarkers including vitamin D [42*], dehydroepiandrosterone sulfate (DHEAS), elevated white cell counts (WCC) [43**], C-reactive protein (CRP) [44], interleukin-6 (IL-6) [45], and C-glycosyl tryptophan [46*], have been identified as predictors of frailty. Such single measures are simple, efficient, and easily accessible in the busy preoperative setting [47].

Pathophysiology

Human aging is a multidimensional process of physiologic decline regulated by genetic, epigenetic, and environmental factors [19, 46*]. In contrast, frailty is characterized by the rapid pathologic impairment of several physiologic and molecular systems [43*]. Evidence suggests that frailty arises when age-related decline occurs synchronously across multiple pathways, thus reaching a critical threshold of dysregulation [45]. Such deterioration depletes homeostatic reserve, rendering the frail patient uniquely vulnerable to perioperative stress and complications [19].

Though the exact pathophysiology remains undetermined, recent literature suggests that at its core, frailty is a pro-inflammatory state. Multiple cross-sectional studies have found that higher levels of inflammatory markers (WCC, IL-6, IL-10, CRP, and tumor necrosis factor) correlate with an increased risk of adverse health outcomes [43**, 45, 48], and are

predictive of postoperative complications (OR = 2.18) [49]. IL-6 in particular has been shown to influence multiple physiologic systems and has been linked to the development of sarcopenia, anemia, and insulin resistance [19, 44, 45].

Emerging basic science research aims to identify specific triggers of this inflammatory cascade. Areas of active research include metabolomics (the study of metabolites within an organism), DNA repair mechanisms, and cellular senescence [19, 46*]. The role of oxidative stress is of particular relevance, as patients are exposed to high levels of reactive oxygen species (ROS) during the perioperative period [50]. Research has demonstrated that via the nuclear factor-κB (NF-κB) pathway, free radicals induce the transcription of inflammatory biomediators and initiate immune dysregulation [51]. Furthermore, ROS alter protein expression, induce DNA damage, and have been implicated as a causative agent in multiple age-related diseases, including cancer, Alzheimer's and cardiovascular disease [51].

In the context of frailty, several studies demonstrate a strong biological link between the inflammatory and endocrine systems [19, 52]. Age-related declines in insulin-like growth factor-1 (IGF-1), DHEAS, and gonadal steroids have been implicated in the pathogenesis of frailty and are thought to contribute to changes in anabolic metabolism and leukocyte function [45, 52, 53]. One recent prospective study of community-dwelling seniors demonstrated that higher baseline cortisol to DHEAS ratios (cortisol:DHEAS) and leukocyte counts were predictive of frailty at 10-year follow up (AUC=0.70) [43**]. This finding is consistent with prior evidence that immune-endocrine dysregulation can induce weakness, declines in skeletal muscle mass, and chronic inflammation [19, 45]. Such translational research is of critical importance and has the potential to guide the development of clinical and pharmacological interventions.

Treatment

Frailty is a dynamic process, and transitions between frailty states are common among the elderly. This is significant because progression from one frailty state to another has considerable impact on patient survival [54]. Though it is possible to clinically improve some markers of frailty, there is a paucity of evidence-based medicine to guide treatment [18, 19]. To date, no clinical trials have investigated whether preoperative intervention can alter or reverse the risk associated with frailty in the surgical setting.

A number of prospective trials from the geriatric medical literature suggest that structured exercise training can improve medical and functional outcomes in the frail elderly [55-58]. It is notable, however, that the greatest benefit is observed in healthier, less frail patients [58, 59]. A recent Cochrane review examining the effect of physical rehabilitation among long-term care residents, found that exercise programs improved functional independence, muscle strength, and gait speed [60**]. Nevertheless, the effect sizes noted were small and it remains unclear if such programs are cost-effective or applicable to the surgical population.

There is limited evidence from the medical literature to support the use of pharmaceutical therapy to modify frailty. Observational studies suggest that angiotensin-converting enzyme (ACE) inhibitors can improve muscle function, boost exercise capacity [61], and slow the

progression of sarcopenia [19]. However, a recent randomized-controlled trial found that treatment with ACE inhibitors did not enhance the effect of exercise training in elderly patients with functional impairment [62**]. A variety of studies have proposed using growth hormone or testosterone to improve muscle mass. Currently, such supplementation is not recommended; and clinical safety and efficacy have yet to be established [63]. Lastly, there is evidence that daily low-dose vitamin D supplementation can reduce sarcopenia, improve muscle strength, and decrease falls among the elderly [64]. However the general use of nutritional supplementation to treat frailty remains controversial, and annual administration of high-dose of vitamin D may actually increase the risk of falls and fractures [65]. Given these findings, future research on optimal vitamin D dosing among medical and surgical patients is warranted [66].

Alternative methods of intervention employ coordinated interdisciplinary teams to mitigate frailty. The primary goal of these teams is to manage geriatric syndromes, develop functional independence, and prevent adverse outcomes [18]. Community-based comprehensive models of care, such as Medicaid's Program of All-inclusive Care for the Elderly (PACE), have been shown to improve physical and cognitive function in community-dwelling seniors [67-69]. Similarly, hospital-based models of interdisciplinary care, such as Acute Care for Elders units, significantly reduce institutionalization [70], 30-day readmission, and cut costs an average of $371 per patient [71]. Such interdisciplinary teams may also be of value postoperatively, as they can aid in the management of geriatric syndromes and guide discharge planning.

Conclusion

There is a growing need for structured and evidence-based preoperative evaluation and risk stratification among elderly surgical patients [4, 8]. Recently, frailty has emerged as a novel independent predictor of operative complications, institutionalization [10, 17], and death [16, 30**, 35**] in this medically heterogeneous and complex population [5]. Current literature suggests that routine preoperative frailty assessment can guide patient selection and has the potential to direct clinical decision-making.

Nevertheless, many questions regarding the role of frailty in the surgical setting remain unanswered. Future clinical trials will be needed to determine the most accurate, efficient, and cost-effective method of frailty assessment. Additionally, biomedical research characterizing the pathogenesis and biologic mechanisms underlying frailty will help guide preventive strategies and drug development and to clarify whether any preoperative interventions may be taken to improve outcomes in this vulnerable population. In conclusion, frailty is particularly relevant to the anesthesiologist's evaluation of the older surgical patient and has the potential to inform perioperative management and ultimately improve outcomes.

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Abbreviations

ACE	angiotensin converting enzyme
ADL	activities of daily living
AUC	area under the curve
CRP	C-reactive protein
DHEAS	dehydroepiandrosterone sulfate
FI	frailty index
mFI	modified frailty index
IGF-1	insulin-like growth factor 1
IL	interleukin
NF-κB	nuclear factor-κB
PACE	Program of All-inclusive Care for the Elderly
ROS	reactive oxygen species
SHARE	Survey of Health Aging and Retirement in Europe
WCC	white cell count

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Key Points

- Frailty is a pro-inflammatory state mediated by dysregulation and decline across multiple physiological systems.
- Frailty is an independent predictor of postoperative complications, institutionalization and death.
- A variety of simple and efficient scoring systems are available to assess frailty preoperatively. However, such methods differ in their prognostic ability and capture different sub-populations.
- There is an emerging potential for preoperative treatment and modification of the frailty syndrome.

Table 1

Frailty Assessment Tools and Scoring Systems in Current Literature

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	Makary et al. [10], Reveing et al. [14**]
Frailty Index/ Deficit Accumulation	30 to 70 measures of comorbidity, ADL, physical and neurological exam	Mortality, institutionalization	Mitnitski et al.[28], Rockwood et al. [29]
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. [25*], Farhat et al. [30**], Karam et al. [31*], Obeid et al. [32*], Patel et al. [23*], Tsiouris et al. [22*], Velanovich et al. [33*]
Gait Speed	5 meter gait ≥6secs	Mortality, major postoperative complications, institutionalization, length of stay	Afilalo et al. [34]
Timed Up and Go	TUG ≤10secs, 11-14secs, ≥15secs	1yr mortality	Robinson et al. [35**]
Falls	6-mo hx of falls	30d major postoperative complications, institutionalization, 30d readmission	Jones et al. [36**]
Robinson	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. [13**, 16]

Notes: ADL (activities of daily living), Cog (cognition), COPD (chronic obstructive pulmonary disease), CVA (cerebrovascular accident), d (days), mo (months), PCI (percutaneous coronary intervention), TIA (transient ischemic attack), TUG (Timed Up and Go), yr (year)