REVIEW ARTICLE

Importance of Frailty Measurement in Oncological Surgery: A Review of Preoperative-Frailty Assessment Tools

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Acknowledgments:
Conflict of Interest: The authors have no conflicts of interest to declare.

Abstract
With the rising number of an aging population, the importance of frailty's impact on perioperative outcomes is increasingly being recognized in the surgical community. Frailty is particularly prevalent in patients undergoing treatment for cancer. In this review article, we seek to summarize the relationship between frailty and oncological surgery and review the preoperative frailty assessment tools available for the practitioner. Due to its predictive value, frailty assessment should be applied within daily clinical practice for those patients undergoing oncological surgery. The choice of a frailty measurement tool seems to be both adaptable and circumstantial. Factors to consider when choosing a frailty measurement tool should include time constraint, patient population, clinical circumstance, resource availability, patient mobility, presence of a self-assessment option, and the statistical requirements/support available for each test. With improved recognition of the diagnosis of frailty, physicians can turn to early interventions aimed at limiting frailty-associated adverse outcomes.

Keywords: Frailty, Frailty Measurement, Postoperative Outcomes

Introduction

An important factor that contributes to adverse postoperative outcomes is a patient's comorbidities. One often overlooked "comorbidity" that has sparked interest in the surgical community is frailty. While the prevalence of frailty fluctuates depending on the measurement tool used, one group noted that 17.4% of adults aged sixty and older were frail and that 49.3% of adults aged sixty or older were considered "prefrail".[1] Handfort et al. performed a systemic analysis of twenty studies focused on oncological patients, and found that over half of the patients were considered prefrail or frail.[2] Recent studies have also demonstrated that age should not be the only surrogate marker needed to assess patients' frailty when considering a patient's risk prior to surgery.[3,4] It is now thought that a frailty measure, rather than a simple age value, should be considered as a better predictor for mortality and morbidity following surgery.[3] With an increasing number of studies outlining the link between frailty and increased postoperative complications, we seek to highlight the important relationship between frailty and oncological surgery. We then review the preoperative frailty assessment tools available for the practitioner.

Frailty in Oncology and Surgery

Oncology

A field of medicine with a particularly high prevalence of frailty is oncology. Complicating this is the fact that the oncologic patient faces a significant amount of physiological stress - both from cancer itself and from combinations of multi-modal treatment involving chemotherapy, radiotherapy, and surgery - eroding the already limited physiologic reserve that exists in frail and prefrail patients.[5] Therefore, the frail oncologic patient often finds oneself at risk for chemotherapy intolerance, progression of disease, postoperative complications, and mortality.[2,5–9]

Surgery

A recent review of twenty-three studies reported that there is evidence to suggest that there is an increased risk of 30-day, 90-day, and 1 year postoperative mortality, complications, and length of stay in frail surgical patients compared to non-frail patients.[3] Another meta-analysis that included sixteen studies and used modified frailty index (mFI) as an indicator for frailty, reported that there were substantial increases in all-cause complications and mortality across a variety of surgical specialties.[10] These authors suggested that a measure of frailty with mFI could be a better predictor for mortality in surgical patients than the widely used American Society of Anesthesiologists (ASA) score.[10]

Oncological Surgery

The importance of frailty in patients undergoing oncological surgery is then paramount given the association of frailty with adverse outcomes both in oncology and in surgery. Particularly, in a study that included forty women undergoing surgical management of gynecologic malignancy, the rate of 30-day postoperative complications in frail patients was 67% whereas those considered non-frail had a complication rate of only 24% ($p=0.04$).[11] Additionally, Krisjansson et al., used a comprehensive geriatric assessment (CGA) tool to predict frailty in patients with colorectal cancer and found that there were not only higher rates of postoperative complications in the frail patient population undergoing operations, but also diminished overall survival.[12] Another study involving the lung cancer patient population demonstrated that frail patients had increased overall mortality (HR 1.57, 95% CI 1.32-1.87) and trended toward increased therapeutic toxicity (OR 2.60, 95% CI 0.82-8.24).[7] Similarly, an

overview of eight studies on gastrectomy demonstrated that frailty was a strong predictor of in-hospital mortality (OR 3.96, 95% CI 1.12-14.09).[13]

The scientific basis for the contribution that frailty plays in adverse medical outcomes in oncological surgery is two-fold. First, frail patients have lower baseline physical reserves, which limit their ability to cope with surgical stress.[6,10,14] Second, on a more cellular level, frail patients often present with higher levels of inflammation thought to be secondary to higher quantities of acute-phase reactants that may inhibit proper wound healing.[10] Overall, frailty risk assessment tools may cue surgeons to improve risk stratification and refine postoperative outcomes.[15]

What is frailty and how can we objectively define it?

While frailty is difficult to define concretely, Leng et al., suggests the following definition: "a clinically recognizable state of increased vulnerability resulting from the aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised."[15] Essentially, frailty may be understood as a decline in a patient's baseline health status that predisposes the patient to adverse medical outcomes when placed under a physiologic stressor, such as surgery. Prefrailty is then the state of being at risk for frailty, but narrowly missing frailty by one of the measurement tools.[5] The topic remains rather subjective and no definition has been widely accepted as the standard.[16] Therefore, it is important to note that the definition of frailty leaves room for subjectivity, making it difficult for practitioners to establish an objective measurement tool that can be widely adopted as the "standard".[16]

How is Frailty Measured?

There are a number of different indices that have been suggested to ascertain frailty.[5,15,17–19] A recent systematic review claimed that greater than twenty different measurement tools exist.[20] The most recent recommendations have supported a more inclusive assessment tool, rather than using a "single-item measurement."[5]

Single-Item Assessment

It was thought earlier that a single value may be predictive of frailty. Some of the single-item assessments that have been studied include the timed up and go test (TUGT), the gait speed test, and screening tests for sarcopenia.[5] The TUGT is one of the simplest ways to assess frailty. To complete this evaluation, a patient must stand up from a seated position, walk ten feet, turn at a marked position, and walk back to return to one's original seated position.[21] Patients are permitted to use assistive devices during this screening test.[21] TUGT values of less than or equal to 10 seconds are considered within normal limits. TUGT values greater than 20 seconds have been associated with increased risk of fall, and have a strong correlation with frailty.[22]

Among the single-item measurement tools of frailty, the gait speed test appeared to be superior in terms of its ability to predict adverse medical outcomes.[23] The gait speed test measures a patient's gait in meters per second. In a study of 2,592 patients, slower gait speed was associated with a higher risk of cardiovascular events.[24] In this study, the optimal cut-off of gait speed was 1.03 m/sec in males less than 70 years of age and 0.94 m/sec in males greater than or equal to 70 years of age. The respective values for women were estimated to be 0.89 m/sec and 0.69 m/sec. [20,24] One study demonstrated that gait speed, however; presents its own challenges. Ibrahim

et al., have pointed out that only 30% of patients were able to walk four meters, limiting the ability to properly assess gait speed in the elderly.[25]

Lastly of the common single-use instrument tools for frailty is a screening test for sarcopenia. Sarcopenia is a clinical syndrome marked by "progressive and generalized loss of skeletal muscle mass and strength."[26] The most efficient way to evaluate sarcopenia clinically is known to be via grip strength.[5,20,25] With lower grip strengths, there is higher all-cause mortality in cancer (demonstrated for colorectal, lung, and breast cancers).[27] Widely accepted grip strength cut-offs are <18.5 kg for men with a BMI ≤24; <20 kg for men with a BMI ≤28, and <22 kg for those men with a BMI >28. The grip strength cut-off values for women are <11 kg for women with a BMI ≤29 and <12 kg for women with a BMI >29.[28]

Due to the complexity and multiple components considered in the diagnosis of frailty, relying on a single-item assessment is not optimal. Their use limitations are promoted by the lack of sensitivity and specificity that arises from the exclusion of additional data points in assessing frailty.[5]

Phenotypic frailty (Freid's Definition)

The phenotypic frailty criteria, as defined by Fried et al., has quickly become one of the more widely utilized assessment tools for determining a common reference of frailty among the preoperative geriatric population. The phenotypic frailty assessment scale attempts to objectively quantify frailty associated with declining energy metabolism and considers the following five criteria: unintentional weight loss, weakness, exhaustion, speed, and physical activity level **(Table 1)**.[29,30] These criteria are interpreted in the following way: patients meeting 1-2 criteria are considered pre-frail and those meeting 3 or more criteria are considered frail.[31] A study reviewing eleven publications employing phenotypic frailty tool found that the risk of postoperative complications in the frail group was higher than the non-frail group (RR 1.6 95% CI 1.60-2.13).[32] This review suggested phenotypic frailty tool to be an appropriate measurement tool for estimating the postoperative complication risk.

Canadian Study of Health and Aging Frailty Index

The Canadian Health and Aging study was a 10-year cohort study initiated in 1991 that assessed the cognitive impairment and health in the elderly. This study reported that an accumulation of deficits acquired with aging negatively impacted one's health and attributed to frailty.[4] In response to this study, the original Canadian Health and Aging Study Frailty Index (CSHA-FI) was developed in 2007. The CSHA-FI is a 70-item frailty index that utilizes aspects of both patient history and physical exam, as well as laboratory values in order to define the factors that impact frailty.[33] Using CSHA-FI in a group of 221 oncologic surgical patients, a recent study found that frailty prior to admission was associated with poor discharge destination (long-term, chronic, or acute care facility) (OR 5.1 95% CI 2.0-13.2).[34]

Table 1: Phenotypic Frailty Assessment*

Unintentional Weight Loss	≥10 pounds within the last year
Weakness	Grip strength in lower 20% based on sex and BMI
Exhaustion	Self-reported exhaustion identified by questionnaire
Speed	Time to stand & walk 15ft; Adjust for sex & height
Physical Activity	Weekly Kcal expenditure based on self-report

*Adapted from: Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M157.

Modified frailty index

The mFI, proposed by Tsiouris et al., is an 11-item adaptation **(Table 2)** of the original 70-item CSHA-FI.[33] While both the CSHA-FI and mFI are based on the accumulation of deficits acquired with aging and their cumulative impact on mortality, the mFI was developed to be more practical for clinical practice. The variables chosen were designed to be obtained through a simple history and physical exam while providing questions that can be answered and quantified in a binary manner.[33] In order to determine a mFI, each variable is equivalent to one point. Once all variables are added the total is divided by eleven resulting in a scale ranging from 0 to 1.0.[35] A proposed patient's mFI score >0.36 indicates frailty.[33] While the mFI has been proven to be effective, a major limitation is inadequate data collection, as the 11-variables utilized are no longer required to be reported by hospitals in the National Surgical Quality Improvement Program (NSQIP) as of 2012.[19] A large study looking at gastrointestinal cancer patients undergoing surgery found that frailty identified using mFI was associated with increased LOS (11.7 vs 9.0 days, $p<0.01$), complications (29.1% vs 17.9%, $p<0.01$), and 30-day mortality (5.6% vs 2.5%, $p<0.01$).[36] This study promoted that increased mFI scores played a significant role in outcome prediction in this oncological surgery population.

Table 2: Modified Frailty Index*

Non-independent functional status
History of diabetes mellitus
History of chronic obstructive pulmonary disease
History of congestive heart failure
History of myocardial infarction
History of percutaneous coronary intervention, cardiac surgery, or angina
Hypertension requiring use of medication
Peripheral vascular disease or rest pain
Impaired sensorium
Transient ischemic attack or cerebrovascular accident without residual deficit
Cerebrovascular accident with deficit

*Adapted from: Ali R, Schwalb JM, Nerenz DR, Antoine HJ, Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery. *J Neurosurg Spine*. 2016;25(4):537-541.

Memorial Sloan Kettering Frailty Index

In response to the limited data available for mFI from NSQIP, researchers at Memorial Sloan Kettering Cancer Center MSKCC developed the Memorial Sloan Kettering Frailty Index (MSK-FI) which was designed to assess frailty based on functional status and comorbidities.[19] The MSK-FI determines a patient's functional status via patient-reported activities of daily living while obtaining information on comorbidities from the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes that had been documented in the electronic medical records from the patient's preoperative appointment to postoperative day two.[19] The MSK-FI is scored by providing 1 point for each evaluated category, totaling 11 points with a score >3 indicative of frailty **(Table 3)**.[19] A study published in 2018 used the MSK-FI to predict increased LOS ($p<0.001$), increased risk of ICU admission (OR 2.34, $p\leq0.01$), and increased overall mortality (HR 1.67, $p<0.01$).[37]

Table 3: Memorial Sloan Kettering Frailty Index*

Functional Status Assessment
Chronic Obstructive Pulmonary Disease or Pneumonia within 30 days before Surgery
Congestive Heart Failure
Myocardial Infarction
Coronary Artery Disease
Hypertension
Peripheral Vascular Disease
Impaired Sensorium
Cerebrovascular Accident
TIA

*Adapted from: Shahrokni A, Tin A, Alexander K, et al. Development and Evaluation of New Frailty Index for Older Surgical Patients With Cancer. *JAMA Netw Open.* 2019;2(5):e193545.

Comprehensive Geriatric Assessment

The CGA is defined as "a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are cataloged, need for services assessed, and a coordinated care plan developed to focus interventions on the person's problems."[38]

In order to complete a CGA, the International Society of Geriatric Oncology recommends the inclusion of functional status, comorbidities, cognitive and mental health, fatigue, socioeconomic and environmental factors, nutrition, presence of geriatric syndromes, and polypharmacy in a thorough patient assessment.[39] CGA is not a definitive or numerical tool, but rather a subjective recommendation of areas that should be assessed while managing the geriatric population. Therefore, there are no set numerical values or scales to reference. A study from Brazil that included 746 patients found that an increase in CGA criteria was directly associated with death while admitted ($p<0.01$), delirium ($p<0.01$), and rate of nosocomial infections ($p\leq0.01$).[40]

While the CGA is considered a complete assessment of frailty in the elderly, limitations such as time commitments and multi-disciplinary cooperation exist and often result in discontinuation of the assessment.[41] Two

methods have been described in order to combat such limitations of the CGA: a 2-step pre-screening process to determine select individuals that will benefit from a more complete CGA and the development of abbreviated CGA tools.[41] Abbreviated CGA tools are brief and fixated on specific elements of the CGA that relate to the topic of interest. An example is the development of the Cancer Specific Geriatric Assessment (CSGA), which successfully measured the domains of functional status, comorbidity, cognition, psychologic, social functioning, social support, and nutrition during patient assessment in-office in an average time period of 27 minutes.[42]

FRAIL Scale

The FRAIL scale is also commonly used in the oncological population, but lacks studies in the oncologic surgical population in particular.[5] The FRAIL Scale is an abbreviated questionnaire occasionally used to assess frailty. It includes five items - Fatigue, Resistance, Ambulation, Illnesses and Loss of weight - resulting in an acronym that is easy to remember and use.[43] The scale ranges from 0-1 with 1 point added for each criterion. The interpretation is such that 3-5 represents frailty and 1-2 represents prefrailty (Table 4).[43]

Table 4: FRAIL Scale*

Fatigue	"How much of the time during the past 4 weeks did you feel tired?"
Resistance	"By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?"
Ambulation	"By yourself and not using aids, do you have any difficulty walking several hundred yards?"
Illness	For 11 illnesses, participants are asked, "Did a doctor ever tell you that you have [illness]?" Illnesses include hypertension, diabetes, cancer, chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease.
Loss of weight	"How much do you weigh with your clothes on, but without shoes?" "One year ago, how much did you weigh without your shoes and with your clothes on?" **Percent change of >5 is scored as 1.

For a "yes" answer, 1 point is given for each component. For the fatigue category scoring is slightly different with responses of "all of the time" and "most of the time" given 1 point.
*Adapted from: Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601-608.

How are Frailty Measurement Tools Used Currently in the Surgical Community?

With the wide range of frailty assessment tools, there is no consensus on a single tool. There is a lack of reproducible results using a certain tool, and there is paucity of literature comparing different tools against one another.[44] The choice of a frailty measurement tool seems to be both adaptable and circumstantial. Factors to consider when choosing a frailty measurement tool should include time constraint, patient population,

clinical circumstance, resource availability, patient mobility, presence of a self-assessment option, and the statistical requirements/support available for each test. Currently, the phenotypic frailty tool appears to be most commonly used.[44] In particular consideration to surgery, the American College of Surgeons as well as the American Geriatric Society have proposed the phenotypic frailty tool to be the best method for preoperative frailty assessment.[44]

Frailty measurement tools can help a practitioner decide whether a conversation needs to be had preoperatively with patients even in regards to minor surgical procedures due to the substantially increased risk profile in those with frailty for all types of operations/procedures. Broadening the frailty screenings will increase the opportunity for these necessary conversations preoperatively.

Preoperative Measures to Counter the Negative Effects of Frailty

With improved recognition of the diagnosis of frailty, physicians can turn to early interventions aimed at limiting frailty-associated adverse outcomes.[45] Once the diagnosis is made, there are multiple options for frailty-related risk mitigation. For example, a correlation between sarcopenia and frailty exists that proposes physical activity as a protective factor.[26] A meta-analysis reviewing eighteen articles concluded that early implementation of a preoperative or pre-therapeutic exercise regimen can improve functional outcomes.[46] Although the types of exercise programs that benefit frail patients the most are understudied, it appears that high intensity exercises are most beneficial.[47] It is thought that exercise has effects on multiple organ systems promoting a positive trend in the sequelae of frailty.[15] In addition to exercise, physical therapy in frail patients undergoing cardiac surgery has been shown to reduce pulmonary complications and to decrease length of stay [5,48]

Another potential intervention in the frail patient population is optimizing his/her nutritional status. Weight loss with resultant sarcopenia is a large component of frailty syndrome. Nutritional optimization has the potential to benefit a patient's functionality, however; direct studies looking at this issue are lacking.[15,18] Additional methods proposed to improve a patient's frailty involve pharmacologic approaches. Different pharmacologic therapies have been proposed, but their benefit is unclear.49 Some drug classes that have been trialed are Angiotensin Converting Enzyme (ACE) Inhibitors, growth hormone, testosterone, and Vitamin D Supplementation. All of the prior mentioned have had mixed results.[49]

Conclusion and Clinical Implications

In the often cited Frailty Consensus, it was determined that current studies support the administration of screening for frailty in all patients aged seventy and older.[16] Other patient populations in which recommendations for screening exist are in those with weight loss of more than 5% with synonymous diagnosis of a chronic illness.[5] We have demonstrated that frailty assessment extends beyond age and takes a multi-system approach in the surgical patient, particularly those with cancer. Thus with its predictive value, frailty assessment should be applied within daily clinical practice for the practitioners who manage patients undergoing oncological surgery.[5]

There is a paucity of studies that compare different frailty screening tools on surgical outcomes resulting in a lack of recommendations regarding which frailty tool

is most applicable/beneficial in the surgical field. Continued research should focus on determining the benefit of each frailty screening tool within a particular patient population and on comparing each scale against its alternatives. Studies should also include the feasibility of implementing frailty measurement tools into the routine preoperative assessment.

Overall, Leng et al., nicely summarized the approach to frailty intervention by stating healthcare personnel should aim to "1) prevent, delay, reverse, or reduce the severity of frailty, and 2) prevent or reduce adverse health outcomes in those whose frailty is not reversible."[14] The International Society of Geriatric Oncology sent out a survey to oncologic surgeons in both the United States and Europe, and reported that only 48% considered routine frailty screening mandatory.[5] Only 25% of them actually administered screening assessments to their patients.[5] Our article highlighted the importance of continual expansion in the application of frailty screening tools to help facilitate early frailty prevention/interventions, and the need to examine the impact of implementing different frailty screening tools available to the practitioner in oncological surgery.

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