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Frailty in Individuals with Genitourinary Conditions*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to characterize frailty, its impacts on clinical care and how to improve outcomes for frail individuals with genitourinary conditions.

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INTRODUCTION

The prevalence of frailty increases with age, ranging from 3% to 45% depending on the age group and population studied.[1-4] Older adults account for roughly half (46.2%) of all outpatient urological visits,[5] making considerations related to frailty particularly important in this population. This Update will review practical considerations regarding the study of frailty among urological populations, including conceptual frameworks, measurement tools for clinical use, current literature on frailty in older adults with urological conditions, and strategies to mitigate risk and improve surgical and treatment outcomes in frail older adults.

CONCEPTUAL FRAMEWORKS FOR UNDERSTANDING FRAILTY

Frailty is commonly referred to as a *geriatric syndrome* representing the loss of physiological reserve. The reduced ability to recover from stressors such as surgery remains distinct and only modestly concordant with multimorbidity and disability, despite the similarities of these conditions.[3] **To that end, the main frameworks to conceptualize frailty as an independent factor are 1) the *phenotypic model* and 2) the *deficits accumulation model*.**

Phenotypic model. This model defines frailty as a distinct physiological process resulting from dysregulation of multiple systems. Fried et al popularized this model using data from the Cardiovascular Health Study.[3] This landmark series leveraged data from an observational study of community dwelling men and women older than 65 years who underwent evaluation at baseline and then yearly during 4-7 years of follow-up. Assessment consisted of examination and surveillance for incident disease, hospitalization, falls, disability and mortality. Based on longitudinal observations, 5 criteria were identified to define frailty (see Appendix).[3, 6] An individual is considered non-frail if 0 criteria are present, pre-frail if 1-2 criteria are present and frail if 3 or more criteria are present.

Using this model, Fried et al further demonstrated that the presence of frailty increases with age, ranging from 3% in those 65-70 years old to 25.7% in those 85-90 years old.[3] They also observed that frailty was most common in older individuals with lower levels of education, lower income, worse overall health status and higher number of chronic conditions. This frailty phenotype has been independently predictive of greater risk of hospitalization, worsening disability, impairments in mobility and death after adjusting for clinical and demographic factors.

Deficits accumulation model. This model defines frailty as physiological vulnerability resulting from an accumulation of multiple unrelated diseases, impairments and health conditions. As more deficits appear, adverse outcomes are more likely due to inadequate recovery from these deficits.

Rockwood et al explored this framework using data from the Canadian Study of Health and Aging, a 5-year prospective study of the prevalence of cognitive impairment and other health issues in a cohort 65 years old or older.[7] Deficits are reported to accumulate at a rate of 3% per year in this group, rising with chronological age.[8] Frailty increased from 70 per 1000 (95% CI 63–78) for those ages 65-74 years to 366 per 1000 (95% CI 306–425) for those 85 years old or older.

Mitnitski et al postulated that health related factors may impact the rate of accumulation of deficits and the time required to recover from them.[8] They operationalized this concept to create a frailty index, a ratio of the number of deficits present relative to the total number of deficits considered. The original frailty index included 70 clinical deficits such as severity of chronic illnesses, ability to complete activities of daily living, and several physical and neurological signs. Later versions consolidated these 70 items into shorter, more parsimonious measures.

FRAILTY MEASURES USED IN CLINICAL ASSESSMENT

While many frailty measures exist, no single instrument is clearly superior for all indications. **Selection of the best frailty measure depends on the setting, available resources and intended use/purpose**.[9] For example the Timed Up and Go Test, which is quick and easy to perform, may be well suited for a busy clinical practice,[10] whereas the Edmonton Frail Scale, a more comprehensive geriatric assessment, may be more appropriate in clinical settings with more resources.[11] This section will detail some of the frailty measures more commonly used in the clinical setting.

Fried frailty criteria. The Fried frailty criteria, as discussed previously, can be easily applied in clinical and research settings to measure frailty in older adults.[3, 12, 13] These criteria were applied in a study of community dwelling individuals 65 years old or older and showed that approximately one-third of the population was pre-frail (28.1%) or frail (8.7%).[13] In this population frail individuals reported poorer health scores, used more health care services, were more likely to have family dependent or limited social support and more commonly endorsed feelings of loneliness compared to non-frail individuals. A separate study of older adults who were hospitalized revealed that roughly half (54.2%) met the Fried definition of frailty.[12] This rate increased to 67.6% in a subset of inpatients 90 years old or older.

Timed Up and Go Test. TUGT is a parsimonious measure of frailty that is relatively quick and simple to administer, making it well suited for use in the clinical setting. To complete this test, the individual is verbally instructed to stand up from a seated position in a chair, walk to a mark 3 meters (10 feet) away on the floor, turn around, walk back and sit down again (see figure). Patients are timed (in seconds) to determine how long it takes to complete this task, and slower times have been shown to correlate with frailty.[14] Individuals are categorized as fast ($\leq$10 seconds), intermediate (11-14 seconds) or slow ($\geq$15 seconds),[10] and these categories serve as proxies for non-frail, pre-frail and frail status, respectively. This test incorporates many important attributes, including core strength, balance, walking speed and

ABBREVIATIONS: OAB (overactive bladder), POPS (Proactive Care of Older People undergoing Surgery), TUGT (Timed Up and Go Test), UTI (urinary tract infection)

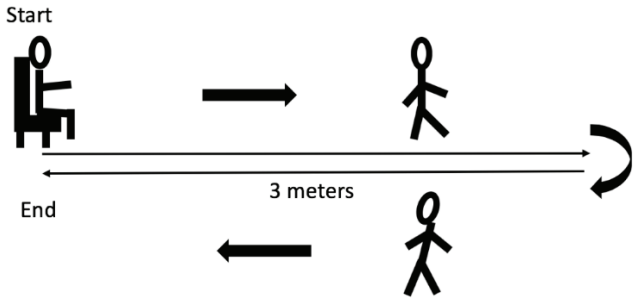

Figure. Timed Up and Go Test.

cognitive ability to follow instructions. TUGT scores may serve as a predictor of changes in functional balance and may also be a useful measure of decline in mobility resulting from deficits across multiple physical domains.[15]

Slower TUGT times are associated with worse postoperative outcomes. One study of patients undergoing colorectal surgery indicated that slower TUGT times were associated with increased rates of postoperative complications (13% in fast, 29% in intermediate and 77% in slow groups, p <0.001) and 1-year mortality (3%, 10% and 31%, p=0.006).[16] TUGT also compared favorably to current standard of care surgical risk calculators at predicting postoperative complications.

In the urological literature TUGT was applied to individuals presenting for care at an academic non-oncologic urology specialty practice.[14] This study showed that 30% of older adults in this population fit into the intermediate frailty category and 15.2% fit into the frail category. The percentage of frail individuals increased with age, with 28.4% of those 81-85 years old and 56.9% of those 86 years old or older being considered frail.

Slower TUGT times were also observed to be independently associated with non-white race in a similar cohort of patients presenting to an academic non-oncologic urology practice (OR 2.5, 95% CI 1.8–3.3, p <0.01),[4] suggesting the potential influence of non-clinical social determinants of health on frailty. Further investigation into the relationship between race and frailty is needed to inform future interventions and methods to combat frailty in diverse populations.

Edmonton Frail Scale. The validated Edmonton Frail Scale is another measure that can be administered by non-specialists in inpatient and outpatient clinical and research settings.[11] This tool was originally developed in a cohort of individuals referred for comprehensive geriatric assessments on acute care wards, rehabilitation units, day hospitals and outpatient clinics in Edmonton, Alberta, Canada. The scale measures cognitive impairment, balance and mobility, mood, functional independence, medication use, social support, nutrition, health attitudes, continence, burden of medical illness and quality of life to link key domains of the geriatric assessment to frailty. The scale uses TUGT to measure functional performance. Identified measures can then be coupled with tailored recommendations to help mitigate risk.

The Edmonton Frail Scale score ranges from 0-17 and is used to stratify patients into 5 levels of frailty, ie not frail, apparently vulnerable, mildly frail, moderately frail and severely frail. Scores correlate with age, gender, numbers of medications, Mini-Mental Status Examination findings and the Barthel Index for Activities of Daily Living. Studies using the scale show good construct validity, reliability and internal consistency.[17]

Studies using the Edmonton Frail Scale also exist in the urological literature. In a prospective observational study the scale was applied to a population of 78 individuals older than 70 years who underwent endoscopic (transurethral resection of prostate or bladder tumor) or open (radical prostatectomy, nephrectomy or cystectomy) urological surgery.[18] The authors characterized the association between preoperative frailty and postoperative complications and observed that 21.8% of patients fit into the frail category and 35.9% fit into the intermediate category. Of those who experienced complications 11.5% were considered frail, 3.8% had intermediate frailty and 6.4% were non-frail (p=0.002). This association remained statistically significant in the endoscopic (p=0.04) and open surgery subgroups (p=0.013).

FRAILTY AND COMMON UROLOGICAL CONDITIONS

Our understanding of the relationship between frailty and specific urological conditions is in its infancy. **Frail older individuals with urological conditions may require additional attention due to the potential impact of frailty on the development of certain conditions and on treatment related outcomes.[5]** Understanding these interactions and the variability relative to the underlying urological condition is important for providing more comprehensive care to older adults.

Frailty and non-oncologic urological conditions. A growing body of literature indicates that frailty may be associated with the presence of certain non-oncologic urological conditions such as overactive bladder and recurrent urinary tract infections. One study using TUGT as a measure of frailty showed that individuals with a diagnosis of OAB had higher average TUGT times vs individuals with other non-oncologic urological diagnoses (mean±SD 13.7±7.9 seconds vs 10.9±5.2 seconds, p <0.0001).[19] This study also indicated that slower TUGT times (indicative of frailty) were significantly associated with a diagnosis of OAB (adjusted OR 3.0, 95% CI 2.0–4.8 for TUGT ≥15 seconds), while age alone was not.

Slower TUGT times are also associated with a diagnosis of recurrent UTIs, with higher mean±SD times of 13.8±10.4 seconds vs 10.8±4.5 seconds in individuals with other non-oncologic urological diagnoses (p <0.01).[20] TUGT times ≥15 seconds are associated with increased odds of recurrent UTI diagnosis (OR 2.0, 95% CI 1.2–3.3, p=0.01) after adjusting for clinical and demographic factors including age.

Collectively these studies suggest that frailty, rather than age alone, is associated with certain non-oncologic urological diagnoses, challenging prior paradigms of OAB and recurrent UTIs as primarily aging related conditions. More research in this area is needed to further explore the implications of frailty in the development, evaluation and management of these common urological conditions.

Frailty and genitourinary malignancies. Prostate Cancer: For older men with prostate cancer selecting the appropriate treatment (surgical or non-surgical) and prognosticating life expectancy and cancer-free survival while preserving quality of life are challenging. This situation becomes even more complex and nuanced among older men who are frail. For example frail older men with high risk, localized disease who, based on cancer stage, may receive the most survival benefit from curative treatment may also be at risk for increased perioperative complications or adverse events.[21] To optimize survival and health related quality of life, urologists must consider how frailty, in

addition to comorbidities, performance status and psychosocial status, may affect estimation of treatment related outcomes.[22] Specifically frailty correlates to increased risk of complications in older men undergoing radical prostatectomy, with one study indicating that those who were more frail preoperatively had increased rates of Clavien grade 4 complications, surgical site infections, reoperations and hospital readmissions.[23] Individuals who are the most frail have significantly greater odds of Clavien grade 4 complications (OR 12.11, 95% CI 2.80–52.35, p <0.005) compared to their non-frail counterparts.[24]

Limited data are available on older and frail older individuals receiving non-surgical treatment for cancer including prostate cancer. A recent systematic review of geriatric oncology trials revealed that less than half (41.5%) incorporated some assessment of comorbidity or frailty.[25] One such study of prostate cancer survivors investigated the relationship between frailty and androgen deprivation therapy exposure.[26] In this survey based series a greater proportion of individuals with current (40%) or past (43%) androgen deprivation therapy exposure were classified as pre-frail or frail compared to those without such exposure (15%, p <0.001). By further exploring the impact of frailty in this population, providers can better estimate perioperative risk and improve oncologic outcomes.

Bladder Cancer: Bladder cancer is a disease of predominantly older individuals, with an estimated 81,400 incident cases and 17,980 deaths projected for 2020.[27] Radical cystectomy, a mainstay of treatment for muscle invasive bladder cancer, is a highly morbid procedure that is associated with increased rates of blood transfusions, acute renal failure, myocardial infarction, reoperation and mortality within 30 days postoperatively.[23] Among older individuals undergoing radical cystectomy frailty has been shown to be associated with increased rates of significant respiratory, renal and cardiovascular complications in addition to higher overall mortality compared to non-frail individuals.[28] Thus, it is recommended that older individuals undergo a comprehensive preoperative geriatric assessment when surgical interventions are being considered.[29] Balancing these perioperative risks with the potential benefits of curative treatment remains challenging, particularly in older adults who are frail.

FRAILTY AND PERIOPERATIVE RISK

Approximately two-thirds of all urological procedures in the United States are performed in individuals 65 years old or older.[5] As discussed previously, frailty is associated with an increased risk of adverse postoperative events such as complications, delirium, prolonged hospitalization, and short and long-term mortality following major surgery.[30-34] **Fortunately, there are several potential actionable points of intervention on the clinical pathway leading to surgery, starting with identification of frailty for preoperative risk assessment and leading to presurgical risk reduction via prehabilitation.**

Risk assessment. Incorporation of a preoperative frailty assessment can potentially optimize surgical outcomes by reducing perioperative risk in older adults. **Identification of frailty can be helpful for preoperative risk stratification and can aid providers in identifying patients who may not be ideal surgical candidates or may be at greater risk for postoperative complications**.[35] Formal recommendations for such assessment have been issued by several professional organizations, including the ACS (American College of Surgeons) NSQIP® (National Surgical Quality Improvement Program), American Geriatrics Society, International Society of Geriatric Oncology and the AUA.[36-38]

The NSQIP/American Geriatrics Society best practices guideline for optimal preoperative assessment of the geriatric surgical patient recommends evaluation and documentation of baseline frailty.[36] While the guideline acknowledges that many frailty measures exist, it promotes 1) the Fried frailty criteria,[3] 2) a definition of frailty introduced by Robinson et al that includes cognitive impairment (Mini-Cog ≤3), poor nutrition (serum albumin ≤3.3 gm/dl), history of falls (1 or more falls in previous 6 months) and low hematocrit (<35%),[16] and 3) a new definition of frailty that includes the addition of functional impairment (TUGT ≥15 seconds and dependence in any activity of daily living) and comorbidity (Charlson comorbidity index score ≥3). The guideline recommends that limitations detected on frailty screening direct further perioperative interventions and more extensive discharge planning.

The International Society of Geriatric Oncology also incorporates frailty into its updated recommendations on the treatment of men with prostate cancer.[37] These guidelines stress the importance of considering biological age and health status rather than chronological age alone when selecting prostate cancer therapy. As a starting point, the society recommends screening with a simplified frailty instrument, the G-8 (Geriatric 8) questionnaire, to identify individuals who may require more comprehensive assessment.[39] G-8 addresses nutritional status, weight loss, body mass index, motor skills, psychological status, number of medications, self-perception of health and age, and can be completed in less than 5 minutes.[40] Based on this instrument, older adults who are noted to be frail with reversible issues may be considered fit for standard treatments, while those with non-reversible health conditions may benefit from further geriatric interventions and tailored treatment plans.[37]

In its white paper, "Optimizing Outcomes in Urological Surgery," the AUA also recommends assessment of frailty as well as functional status, cognitive impairment and delirium prevention for older adults considering urological surgery.[38] This evaluation of surgical fitness is promoted to be useful in the preoperative setting to help counsel, risk stratify and potentially risk modify older patients considering urological surgery.

Integrating a frailty risk assessment protocol into clinical practice can take many forms. Implementation may vary considerably based on the resources available and the type of clinical practice. One potential action would be to include a frailty questionnaire in the initial intake paperwork completed by new patients. This information could then be incorporated into the history taking portion of the encounter. In larger practices clinic staff can administer the TUGT after obtaining vital signs with little impact on clinic workflow.[10] Reporting the results of the frailty screening in the clinical note generates a record of degree of frailty at each encounter. The prospectively collected frailty scores can then be entered into a clinical database if the infrastructure exists within the medical system.

Preoperative risk reduction measures and prehabilitation. Once a patient has undergone preoperative screening and is identified as frail, this information can be used as an opportunity to help mitigate risk via preoperative prehabilitation. With prehabilitation providers can tailor perioperative management for frail individuals with a comprehensive assessment and initiation of interventions aimed to improve preoperative/baseline

functional status or fitness. **Prehabilitation can improve the functional capacity of patients to reduce the risks of morbidity or mortality attributable to frailty.** Multidisciplinary programs focused on prehabilitation can encompass multiple domains including exercise, nutritional education and psychological interventions to improve outcomes.[41]

Hall et al examined the effect of a frailty screening initiative, in which they performed frailty assessments in patients scheduled for major elective non-cardiac surgery at a Veterans Affairs medical center using the Risk Analysis Index.[42] Cases that screened positive for frailty were flagged and reviewed by a team of surgery, anesthesia, critical care and palliative care clinicians, and care plans were modified based on team input to clarify surgical decision making and optimize perioperative care. As a result of this screening and multidisciplinary input, rates of 30-day overall mortality in frail patients decreased from 12.2% to 3.8%.

A separate study engaged individuals in 4 domains (walking, breathing, nutrition and stress management) as part of a prehabilitation program before major abdominal surgery.[43] Those enrolled in the program were shown to be less likely to require blood transfusion intraoperatively or intensive care unit admission postoperatively, and ultimately had lower overall hospital charges compared to their counterparts without preoperative prehabilitation.

The POPS (Proactive Care of Older People undergoing Surgery) program combined preoperative comprehensive geriatric assessments with postoperative follow-up for 108 at risk older adults undergoing elective orthopedic procedures.[44] Preoperative risk screenings revealed that more than a third of the cohort (38.5%) had at least 2 risk factors for poor postoperative outcomes and almost three-quarters (72.8%) experienced social isolation. Half of the cases were managed by the POPS program and the remainder by usual care (pre-POPS). For the study intervention the POPS team, composed of a consultant geriatrician, geriatric nurse specialist, occupational therapist, physiotherapist and a social worker, collaborated to identify and minimize medical comorbidities, predict and plan discharge requirements, coordinate discharge care or intermediate care and provide patient education in the preoperative setting. Postoperatively the team aided in early detection and management of medical complications, early mobilization, pain management, treatment of bladder-bowel dysfunction, and nutrition and discharge planning. After discharge the POPS team provided follow-up home and outpatient clinic visits.

Postoperative complications including delirium, pneumonia and wound infections were significantly less common in the POPS intervention group vs the pre-POPS group ($p < 0.05$ for all).[44] Additionally the POPS interventions resulted in improvement in pain control, early mobilization, reduction in inappropriate catheter use and shorter hospitalizations. The authors concluded that many of the postoperative complications were preventable, provided patients underwent the appropriate interventions.

Another study, the Michigan Surgical Home and Optimization Program, enrolled patients in a structured preoperative regimen that combined training in walking, breathing, nutrition, stress management and smoking cessation.[45] Participating individuals demonstrated significantly greater physiological variability in systolic and diastolic blood pressure, fewer operative complications, decreased rates of intensive care unit admission, reduced rates of perioperative transfusion and lower total hospital charges compared to non-participants.[43] Based on these findings, the authors concluded that the benefits of such a program are multifactorial, particularly in frail patients who are deconditioned and at greater risk for complications.[45]

While prehabilitation programs may serve as an effective preoperative intervention to reduce risk before a major surgery, they require timely and efficient frailty characterization and risk assessments. Prehabilitation by sending patients to the appropriate providers can aid in addressing deficits, even in settings that lack a formal prehabilitation program. The Edmonton Frail Scale can be helpful in identifying domains of frailty that lend themselves to actionable prehabilitation items.

CONCLUSION

Frailty represents an under considered and under diagnosed syndrome with the potential to significantly impact outcomes for individuals with many types of urological conditions. Numerous instruments exist for the purpose of identifying those at risk for frailty and quantifying the potential impact. A comprehensive geriatric assessment that includes frailty status can aid in risk stratification. Early detection and focused interventions such as prehabilitation can further help mitigate the potential harmful effects of frailty in the perioperative setting to reduce perioperative risks and improve care for frail older individuals with urological conditions.

DID YOU KNOW?

- Two main frameworks to describe frailty exist: the phenotypic model and the deficits accumulation model.
- While various frailty measures exist, selection of a particular measure should depend on the setting, resources and intent of frailty measurement.
- Frailty prevalence varies with the cohort studied, and the effects are heterogeneous.
- Preoperative surgical risk assessment should incorporate frailty measurement for risk stratification and risk reduction/mitigation.
- Multidisciplinary interventions and prehabilitation strategies can improve outcomes for frail older adults undergoing invasive urological procedures.

Appendix. Fried phenotypic model of frailty using 5 criteria[3,6]

Domain	Definition
Unintentional weight loss	10 lbs or greater weight loss in past year
Exhaustion	Self-reported poor endurance and energy based on Center for Epidemiologic Studies Depression Scale
Weakness	Grip strength in the lowest quintile, adjusted for gender and body mass index
Slow walking speed	Slowest 20% of the population based on time to walk 15 feet, adjusted for gender and standing height
Low physical activity	Lowest quintile of physical activity reported, adjusted for gender, based on a weighted score of participant reported kilocalories expended per week at baseline

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Study Questions Volume 39 Lesson 17

1. The deficits accumulation model is different from the phenotypic model because it
   a. relies on additional domains to be used compared to the phenotypic model
   b. focuses on disease rather than general domains
   c. considers how long it takes to recover from physiological insults
   d. considers the accumulation of deficits and how one recovers from physiological insults

2. TUGT times in non-white compared to white patients in an academic non-oncologic urology specialty practice are
   a. faster
   b. slower
   c. not significantly different
   d. unknown

3. Independent of age, an individual with a diagnosis of OAB and recurrent UTIs is likely to have a TUGT time of
   a. ≤10 seconds
   b. 11–12 seconds
   c. 13–14 seconds
   d. 15–16 seconds

4. An 80-year-old retired cyclist with hypertension and muscle invasive bladder cancer is considering radical cystectomy. The next step is
   a. prescribe additional anti-hypertensive medication to normalize his blood pressure
   b. perform a comprehensive geriatric assessment to estimate perioperative risk
   c. counsel the patient to consider alternative treatments
   d. discuss palliative therapy

5. A prehabilitation program or prehabilitative interventions lead to
   a. increased health care spending
   b. higher rates of urinary catheterization
   c. early detection and management of medical complications
   d. no change in patient reported outcomes

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