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Frailty - 50 Years of Study, 50 Frailty Instruments, Proofs of Benefit

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ABSTRACT

Frailty is a geriatric syndrome characterized by age-related decrease in functional reserves and function, involving multiple organs and systems, resulting in amplified vulnerability to stressors, and an increased risk of adverse outcomes. Diagnosing frailty informs about a person's general health and the hazards when exposed to disease, invasive diagnostic or therapeutic procedure. To diagnose frailty instruments were developed, tailored to different patient populations and different purposes: in screening for frailty, patient triage, assessment of perioperative risk, care planning, avoidance of deconditioning during illness. In being fitted to population and clinical setting, a frailty instrument is valuable under the defined circumstances; it may be inadequate if applied to different settings. Based on the vast literature and personal experience in practice, we outline positive matchings between diagnostic purpose and frailty instruments selected out of the more than 50 existents. There is given emphasis on generally accepted guidelines for frailty diagnosis and management, as well as on recent developments proposing molecular chemistry and artificial intelligence in diagnosing and monitoring frailty.

Keywords

Geriatric, Frailty, Disability, Multimorbidity, Ageing.

Introduction

The aging process is heterogeneous. Healthy aging describes a good aging course, contrasting with the state of older people having chronic diseases, functional impairment, and disability. Geriatric syndromes describe common conditions in older adults that involve multiple body systems rather than a single specific disease [1]. Among geriatric syndromes, frailty signifies multisystem vulnerability. Frailty is a geriatric syndrome characterized by an age-dependent decrease in functional reserves involving multiple organs and systems, resulting in increased vulnerability to stressors and an increased risk of adverse outcomes [2]. A common stressor such as infection, trauma, ischemia or even social crisis may trigger a cascading succession in failure of metabolic systems, physical functioning, cognition and behavior, the loss of activities of daily living, falls and fractures, depression, hospitalization, and mortality [3-9]. The concept of frailty being defined as a decrease in physiological reserves, is widely accepted though the biological pathways to frailty have not been fully elucidated [10]. Physiological reserves are lost during ageing, but not to the same degree in different organs and systems, and not in the same rate amongst individuals. The inequality of ageing across different organs is a feature of healthy ageing but becomes more pronounced as diseases, environmental exposures, and genetic predisposition may affect individual organs. *Primary frailty* denotes that frailty results from aging and *secondary frailty* denotes that frailty results from the effects of various specific disorders. So, a person's medical history may shape the threshold of frailty and determine the frailty phenotype. There was recent progress in elucidating molecular mechanisms underlying frailty [11]. Importantly, physical exercise that improved the functional status of frail patients also impacted and reversed frailty biomarkers [12].

Frailty phenotypes have been classified under the categories of physical [13-16], cognitive, and social [17-19]. Such variety of frailty syndromes have instigated development of more than 50 instruments for diagnosing frailty, and no agreed standard for

frailty measurement exists. Different frailty instruments are based on different concepts of frailty and mostly are not interchangeable [20]. Though unified as a concept, no single instrument is considered the gold standard for assessment and measurement of frailty [10].

Frailty diagnosis

Two basic models are widely used to assess frailty, the phenotypic model and the deficit accumulation model. Examples are shown in the following. *The physical phenotype model of Fried* [15] comprises five criteria: 1. weight loss (the involuntary loss of >5% of body weight in the last year), 2. fatigue/exhaustion (an answer of 'yes, often or chronically' to the question 'In the past week, do you feel that you are unable to gather your energy to do things?'), 3. weakness (handgrip strength in the lowest 20% of normal range adjusted to gender and BMI, reflected by having difficulty in grasping or turning objects), 4. slowness (slower than 20% speed adjust for gender and height), and 5. low physical activity (difficulty performing at least one of the following activities: bathing, dressing and undressing, feeding, getting out of bed, standing up, sitting on a chair, walking, and toileting). A person is considered frail if three or more of these criteria are met.

The frailty index model of Rockwood [21] of cumulative deficits represents an accumulation of health deficits Domains include: physical measures (such as handgrip strength, gait speed, and BMI), co-morbidities, disabilities (activities of daily living (ADL) and instrumental ADL (IADL)), psychological variables (including depression and anxiety), symptoms of frailty such as weight loss and exhaustion, and poor self-reported health.

The Rockwood Clinical Frailty Scale [14] a judgment of a person's general health status by inspection of nine illustrations to which the patient's appearance is compared. Based on pictures and corresponding text a judgement of the health status is made on a scale from 1 to 9: the lowest score of 1 is the label for a very fit person and the highest score 9 designate the terminally il. The *FI-MDS* [22] is derived from the Resident Assessment Instrument-Minimum Data Set 2 document: a list of 58 deficits was derived representing multiple functional domains. Each deficit was assigned either 0 (absence of the condition or attribute) or 1 (presence of the condition or attribute). It is expressed as a ratio of the number of deficits present to the total number of 58 deficits considered. The more deficits an individual has, the greater the risk of adverse outcomes is considered. *The FRAIL scale* addresses and scores five domains: Fatigue (feeling tired most of the time in the last 4 weeks), Resistance (difficulty walking up 10 steps without resting), Ambulation (difficulty walking several hundred yards), Illness (having five or more of the following arterial hypertension, diabetes mellitus, cancer, asthma, arthritis, heart disease), and Loss of weight (more than 5% of body weight in the past year). One point is granted for positive answering each question. Score 0 points matches robust health, 1–2 points make out a pre-frail state, and 3–5 points signify frailty [23]. *The Edmonton Frail Scale* is an 11-item scale, of which 9 items are self-reported and two items are administered by a trained medical personal: a cognitive screen (clock-draw), a functional screen (Timed Get up and Go). For each of the 11 domains 0, 1, or 2 points are assigned. The self-reported domains include the general health status, independence, polypharmacy, nutrition, depression, incontinence. Scores 0 to 5 are interpreted not frail, 6 to 7 is vulnerable, 8 shows mild to severe frailty. It takes 3 to 5 minutes to complete and is reliable in assessing frailty among older adults in stable clinical condition or community settings, yet, caution is necessary when applying the tool in acutely ill patients [24].

The Multidimensional Prognostic Index (MPI) [25] is a validated clinical tool based on a comprehensive geriatric assessment. It evaluates an older patient's risk of short- and long-term mortality, length of hospital stays, and institutionalization by measuring eight domains: functional, cognitive and nutritional status, cohabitation status, comorbidities, polypharmacy and risk of pressure sores, using validated rating scales. The MPI generates a numeric score between 0 and 1 that expresses the global risk index of multidimensional impairment. MPI subdivided into three risk groups: MPI1, 0-0.33 = low risk, MPI2, 0.34-0.66 = moderate risk and MPI3, 0.67-1, severe risk.

Operationalizing frailty is challenging particularly in those unable to undergo performance-based tests or self-report impairments. The request that a frailty tool should be quick, reliable, and easy to use in clinical settings guides our personal preference for Rockwood Clinical Frailty Scale and the FRAIL scale.

Different frailty tools for different target populations

Validity of a frailty tool depends on the target population to which it is intended, the health care setting (primary care, secondary or tertiary care), the health outcome of interest, the time frame of follow-up, and the settings to be used either in research or in clinical practice. Certain frailty tools are suitable for population screening; others are used as predictors of adverse clinical outcomes. For example, the multidimensional prognostic index (MPI), that originally was developed as an index to predict mortality in older hospitalized patients [25], came in use to predict negative health outcomes in heart failure, myocardial infarction, chronic kidney disease, pneumonia, acute respiratory failure), COVID-19, dementia, and cancer [26,27]. The diagnosis of frailty has been used to assess risks, design individualized care, and guide shared decision-making, including recommendation for palliative care [28-31].

Prediction of frailty-related risk

Frailty as a predictor for hazard ratios is informative, but better prediction models are needed when considering the choice between two treatments, for example to do or to abstain from an elective surgical procedure, or the decision in favor of aortic valve replacement versus transcatheter aortic valve repair. Potentially useful prediction models are considered having Area Under the Curve (AUC) >0.80, while values below 0.80 are considered of limited utility [32]. Indeed, the accuracy of a frailty tool in

discriminating between binary outcomes can be measured by integrating sensitivity and specificity in the AUC. The AUC provides a measure of diagnostic accuracy ranging from random chance (AUC 0.5) to perfect accuracy (AUC 1.0). Specifically, frailty tools demonstrating AUC >0.80 are potentially useful in clinical decision making. In our review of the literature most frailty tools showed AUC less than 0.80 in studies with different patient populations and different clinical settings [23,33-36]. As in the above quoted, and numerous other studies in the literature, our personal experience was disappointing. We assessed whether the outcome of rehabilitation after a proximal hip fracture can be predicted by degrees of frailty before the fracture. The FI-MDS frailty index and the Clinical Frailty Scale were used as comprehensive measures of the patients' health status before hip fracture. The Functional Independence Measure (FIM) on discharge served as a measure of rehabilitation outcome. Both frailty tools, the FI-MDS and Clinical Frailty Scale, fitted well to the study, since the patients' physical and cognitive limitations were impeding on performance of motor tests and in some cases also on self-reporting. Both pre-fracture frailty instruments correlated strongly ($p < 0.0001$) with FIM discharge score ≥90, i.e. success of rehabilitation. However, their predictive accuracy was disappointing: the best discrimination of successful rehabilitation vs. failure was provided by FI-MDS with 88.5% sensitivity but merely 53.8% specificity. Beyond common sense used in first triage, frailty tools performed with insufficient specificity in predicting outcome of rehabilitation [37]. *Specially devised frailty instruments* for preoperative risk assessment may perform better than standard frailty tools. So, an ad-hoc developed "Modified Frailty Index (mFI)" was used as a surrogate for frailty to predict morbidity and mortality after laparoscopic cholecystectomy for acute cholecystitis [38]. The mFI differs remarkably from common frailty tools by the 11 parameters it comprises: patient's functional status, diabetes mellitus, hypertension requiring treatment, myocardial infarction, prior cardiac surgery or percutaneous coronary angioplasty or history of angina, chronic obstructive pulmonary disease or pneumonia, rest pain or gangrene secondary to peripheral vascular disease or treated with angioplasty, revascularization, amputation; impaired sensorium within 48 hours prior to the surgical procedure not in the context of concomitant neurologic disease such as dementia; history of transient ischemic attack or cerebrovascular accident without neurologic deficits; and cerebrovascular accident with neurologic deficits. The mFI in predicting morbidity and mortality after laparoscopic cholecystectomy for acute cholecystitis study showed excellent accuracy for mortality (AUC = 0.83) and less so for Clavien IV complications (AUC = 0.73). Other investigators developed a prediction model to assess the one-year and two-year mortality after transcatheter aortic valve implantation [39]. In analyzing predictors of mortality in a large cohort of patients, the model integrated three independent predictors: the clinical frailty scale (Rockwood), presence of atrial fibrillation, and tissue-inhibitor of metalloproeinase-1. Their sum-score permitted to separate a low-risk from a high-risk group. Survival analysis showed a significant ($p < 0.001$) survival benefit for the low-risk group after one and two years.

A frailty assessment tool based on machine learning for clinical risk prediction [40] integrated the following parameters: age, sex, body mass index, pulse pressure, creatinine, hemoglobin, preparing meals difficulty, and lifting/carrying difficulty demonstrated robust predictive power. The algorithm (XGBoost) exhibited high performance on internal validation (AUC 0.94) and external validation (AUC 0.85). It showed superiority to customary frailty indices in predicting cardiovascular events, progression of chronic kidney disease and mortality.

The Frailty Care Bundle

The Frailty Care Bundle is designed for hospitalized elderly patients with acute illness to reduce the risk of deconditioning and functional decline. During an acute infection, trauma, elective surgery, coronary events or other acute events, not only is the primary target organ at jeopardy but the whole body is exposed to deterioration. So, the multisystem, nonspecific consequences of acute disease may be acute sarcopenia, delirium and cognitive deconditioning (even in patients who do not develop delirium), constipation, urinary retention and infection, orthostatic hypotension, and pressure ulcers. These deleterious effects of hospital-associated deconditioning may be temporary or long lasting [10,41]. Hence, preventative strategies should be used involving a multidisciplinary approach, such as the Frailty Care Bundle. Essential to this goal is the multidisciplinary team are geriatric-trained nurses and physicians, dieticians, physiotherapist and an elderly-adapted ward equipment and furniture. The core interventions are early mobilization, early and adequate and nutrition, delirium screening and prevention, cognitive stimulation, and good communication between staff, patients and relatives. All these preventive interventions (the bundle) should be applied to all elderly hospitalized persons, whether in good health condition at baseline or frail. Among all, the frail elders may benefit most of measures aimed at preventing deconditioning. Hence, identification of frailty on admission can help in assessing the risk of hospital-associated deconditioning and referring those who could most benefit to specialized older persons' wards [41]. Multicomponent intervention is cost-effective by reducing adverse events and length of hospital stay [42,43].

Guidelines

While diagnostic limitations of frailty instruments in clinical practice are recognized [10,44], their judicious use, directed to specific clinical settings and target populations is highly recommended. Clinical practice guidelines have been designed for these aims, including recommendations for screening and recommendations for management of patients with frailty. It is advocated that health practitioners screen all older adults for frailty periodically, using a validated frailty tool that is suitable for the specific setting in the community. In addition, during general consultations for acute medical illnesses, clinicians should be alert to potential frailty signs. Individuals screened as positive for frailty should undergo a comprehensive clinical assessment to address treatable causes and deficiencies. A broad care plan should address organic, psychological and social factors such as overt or occult heart failure, respiratory failure, chronic inflammation,

malnutrition, weight loss, hypo- or hyperthyroidism, anemia, vitamin B12 deficiency, depression, sarcopenia, abnormal stance and gait, disorders, polypharmacy, and social support. First-line therapy for frailty should include a physical activity and exercise program, healthy diet with protein/caloric supplements as needed. No systematic recommendation was given for vitamin D supplementation, hormone-based treatment, and cognitive therapy. Regular checkups are recommended. So far, there are no medications for treating frailty [10]. These general recommendations for managing patients with frailty are intended equally as preventive measures for healthy elders, for prefrail persons, for persons with mild, moderate or severe frailty, as well as for elders with multimorbidity. Screening for frailty and applying its management guidelines may also be valuable, even in patients with severe organ failure, complex psychogeriatric morbidity and in palliative care (Table 1).

Table 1: Frailty screening: when and by which tool.

Instrument	Purpose	Setting
Physical frailty instrument*	Annual health screen	Community
FRAIL **	Triage	Emergency room
Specially tailored tools	Procedural risk assessment	Hospital
Frailty Care Package	Prevention of deconditioning	Hospital
Palliative care package	Shared decision making	Palliative care

*e.g. Fried's frailty instrument, ** e.g. the FRAIL scale.

In conclusion, while most frailty instruments were originally designed for research purposes, over the years they were adopted for frailty case finding, patient triage, care planning, and perioperative risk assessment. Different frailty instruments are based on different concepts of frailty, suited to different populations, and are not interchangeable. In perioperative risk assessment, specially designed frailty tools outperform the commonly used Fried's frailty phenotype, Rockwood and Mitnitski's Frailty Index. Appliance of artificial intelligence in tailoring personalized frailty tools may further improve clinical decision making in elders. The recently adopted Frailty Care Bundel is designed for hospitalized patients to reduce the risk of deconditioning and functional decline. Identifying biomarkers qualified to predict frailty might assist in developing strategies to preserve functional reserves and health. Screening for frailty and applying its management guidelines may be valuable in the large spectrum of general elderly population, those with organ failure, psychogeriatric disorder and even in palliative care.

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