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Frailty: What does it mean for Clinical Care Provision?

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ABSTRACT

This article forms part of the Approaching Geriatric Patient series. Speaking to medical and nursing students, it is common to see and be asked to assess frail older adults on medical and surgical wards. However, there is great uncertainty about how these older adults should be managed. It is common that students ask what aspects of frail patients' care should and could be different compared to other patients to improve quality of life and optimise clinical care for this increasing patient group. The objectives of this review are: (1) to briefly outline the main operationalisations of frailty that are suitable for clinical care provision; (2) to review the use of frailty tools in 'aggressive' therapeutic areas such as surgery and oncology; (3) to review the evidence for the role of frailty in the assessment of traditional cardiovascular risk factors and the more appropriate prescribing of medications; and (4) to make a case for frailty as a screening tool for access to evidence-based comprehensive geriatric assessment (CGA) services.

Key words: Frail elderly; risk assessment; individualized medicine; evidence-based medicine.

Introduction

'Frailty' is a commonly used term outside and inside Medicine. The definition of *frail* adjective from the Cambridge Advanced Learner's Dictionary & Thesaurus (http://dictionary.cambridge.org/dictionary/british/) is:

'*Weak or unhealthy, or easily damaged, broken, or harmed*'

Indeed, frailty is about **vulnerability** to poor resolution of homoeostasis after a *stressor event* and is a consequence of cumulative decline in many physiological systems during a lifetime.[1]

Campbell & Buchner defined frailty as 'a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure; and as a consequence the frail person is at increased risk of disability and death from minor external stresses'.[2]

In the context of clinical care provision, frail older adults represent a challenge to clinicians because they usually present with an increased burden of symptoms, are medically complex, and less able to tolerate interventions of any kind (more prone to complications). In addition, patients who are frail have more subtle signs and symptoms that can be easily overlooked.

In clinical care provision, some interventions can be more 'aggressive' than others and hence be more complication-prone. Frail (vulnerable) adults are more likely than 'robust' adults to suffer complications from a given medical intervention. While 'fit' people are resilient and 'frail' people are vulnerable, chronological age *per se* cannot tell where a person is along the 'fitness-frailty' spectrum[3, 4], due to the great *biological heterogeneity* of the population of older people.[5] Frailty more closely relates to the *biological* than to the *chronological* age of individuals.[6, 7]

The measurement of frailty *as a surrogate for vulnerability* in healthcare delivery is therefore of utmost importance in a current world characterised by an ageing population and continuing efforts to not only prevent and minimise iatrogenic events, but also concentrate the use of public resources in interventions for older people that are *effective* and *evidence-based*.

The objectives of this review are: (1) to briefly outline the main operationalisations of frailty that are suitable for clinical care provision; (2) to review the use of frailty tools in 'aggressive' therapeutic areas such as surgery and oncology; (3) to review the evidence for the role of frailty in the assessment of traditional cardiovascular risk factors and the more appropriate prescribing of medications; and (4) to make a case for frailty as a screening tool for access to evidence-based comprehensive geriatric assessment (CGA) services.

As an intuitive concept, frailty (i.e. vulnerability) is well recognised clinically. However, the objective measurement (i.e. operationalisation) of the concept is still a matter of debate and there is no agreed gold standard. Instead, there are several definition approaches, two of the most popular being the frailty *phenotype* (i.e. frailty as a *syndrome*) and the frailty *index* (i.e. frailty as a *state*). Rather than being competitive or mutually exclusive, both approaches are actually complementary and suitable for different purposes or scenarios.[8]

A Common Operationalisation of Frailty: The Frailty Phenotype

According to the phenotypic approach, frailty is defined as a clinical *syndrome* in which three or more of the following criteria are present: *unintentional weight loss*, self-reported *exhaustion*, *weakness*, *slow walking speed*, and *low physical activity*.[9, 10] This approach defines two additional states: pre-frail (i.e. one or two criteria present) and non-frail (i.e. none of the criteria present). According to the biological theory underpinning the frailty phenotype, co-morbidity is a risk factor for frailty, and frailty is a precursor of disability.[11] The original validation of this approach by Fried *et al*. included significant associations with incident disease, hospitalization, falls, disability and mortality, independently of chronological age.[10] Table 1 shows

the original frailty phenotype criteria as defined in the *Cardiovascular Health Study*.[10]

Table 1. Phenotypic frailty criteria.[10] Positive for frailty phenotype: ≥3 criteria present; intermediate or prefrail: 1 or 2 criteria present. Robust or non-frail: no criteria present.

- **Weight loss:** unintentional weight loss of more than 10 pounds (4.5 Kg) in the last year.

- **Exhaustion:** for at least 3 days in the last week, "I felt that everything I did was an effort" and/or "I could not get going".

- **Physical Activity:** Based on the short version of the Minnesota Leisure Time Activity questionnaire.[12]

  Men: Those with Kcals of physical activity per week <383 are frail by this criterion.

  Women: Those with Kcals per week <270 are frail by this criterion.

- **Walk Time**, stratified by gender and height:

Men	*Cut-off for Time to Walk 15 feet (4.6 m) criterion for frailty*
Height ≤173 cm	≥7 seconds
Height >173 cm	≥6 seconds
Women	
Height ≤159 cm	≥7 seconds
Height >159 cm	≥6 seconds

- **Grip Strength**, stratified by gender and body mass index (BMI) quartiles:

Men	*Cut-off for grip strength (Kg) criterion for frailty*
BMI ≤24	≤29
BMI 24.1–26	≤30
BMI 26.1–28	≤30
BMI >28	≤32
Women	
BMI ≤23	≤17
BMI 23.1–26	≤17.3
BMI 26.1–29	≤18
BMI >29	≤21

Because surrogates for individual frailty phenotype criteria are possible [13], there have been attempts to provide healthcare practitioners with phenotypic frailty assessment tools that do not require *post-hoc* calculations and can be scored immediately after an individual assessment. An example is the Frailty Instrument for Primary Care of the *Survey of Health, Ageing and Retirement in Europe* (SHARE-FI) [14]. This tool is based on a modified phenotypic approach and includes two web-based frailty calculators (one for each gender) that are freely accessible on *BMC Geriatrics* (http://www.biomedcentral.com/1471-2318/10/57/additional). Their use is intended for community-dwelling adults aged 50 and over. Translated versions of

the calculators can be accessed on https://sites.google.com/a/tcd.ie/share-frailty-instrument-calculators/. SHARE-FI has been validated against incident disability [15] and mortality.[16] In an observational study, a recent study showed that people identified as frail by SHARE-FI had worse physical performance scores, more history of falls, more medication burden, and were more often referred for ongoing assessment and rehabilitation [17]. An advantage of SHARE-FI is that, on average, it takes about 6.5 minutes to administer (http://www.uakron.edu/dotAsset/8b117eba-ec49-4e57-9495-fe41fcfbd995.pdf).

Another Common Operationalisation of Frailty: The Frailty Index

A way to operationalise frailty is by considering it *as a state* and counting in an individual the number of *deficits* that he/she has accumulated from a given list (of usually 30 or more potential deficits). Deficits are widely defined as symptoms, signs, diseases and disabilities that accumulate with age.[18] The number of counted deficits divided by the number of deficits considered results in a score called *frailty index* (FI), which ranges from 0 (none of the deficits present) to 1 (all deficits present).

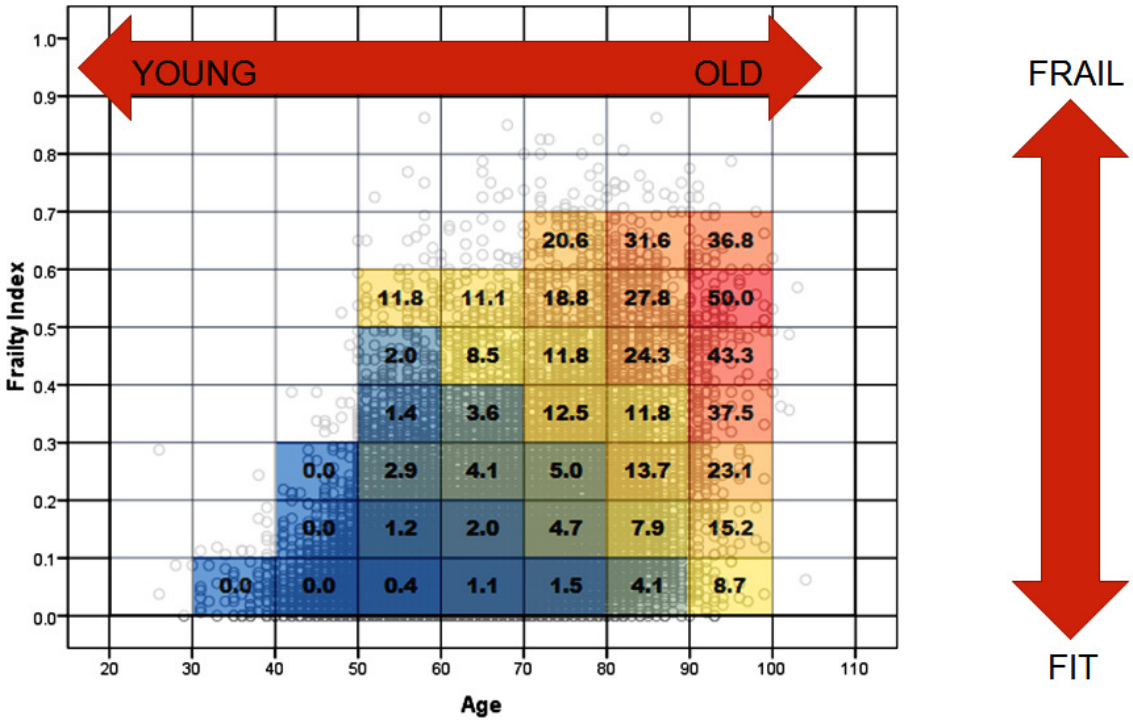
The construct validity of the FI is examined through its relationship to chronological age, and its criterion validity is examined in its ability to predict mortality [19], and in relation to other predictions including disability and use of healthcare resources [20]. Table 2 and Figure 1 exemplify a 40-item FI validated in the *Survey of Health, Ageing and Retirement in Europe* (SHARE).[20]

Table 2. 40 items for a frailty index in SHARE.[20]

Difficulties: bathing or showering	Difficulties: lifting or carrying weights	Moderate or vigorous physical activity: hardly ever, or never	High blood pressure	Hip or femoral fracture
Difficulties: dressing	Difficulties: shopping for groceries	Diminution in the desire for food and/or eating less than usual	Heart attack	Impaired orientation to date, month, year and day of week
Difficulties: getting up from chair	Difficulties: doing work around the house or garden	Poor self-perceived health	Stroke	Body mass index (Kg/m^2) deficit
Difficulties: walking across a room	Difficulties: preparing a hot meal	Long-term illness	Cancer	Breathlessness
Difficulties: eating, cutting up food	Difficulties: taking medications	Fatigue	Diabetes	Falls

Difficulties: reaching or extending arms above shoulder	Difficulties: managing money	Sad or depressed	Arthritis	Fear of falling
Difficulties: using the toilet	Difficulties: walking 100 metres	Lack of enjoyment	Chronic lung disease	Dizziness, faints or blackouts
Difficulties: climbing one flight of stairs	Difficulties: getting in or out of bed	Hopelessness	Osteoporosis	Grip strength (Kg) deficit

Figure 1: Association of the SHARE frailty index with mortality (mean follow up: 2.4 years) by age decade and tenth of FI, in SHARE wave 1 (men and women combined, total *N* = 20,547). The number on each coloured cell represents the mortality rate (%) for that cell.



In terms of individual risk stratification, the FI is a continuous variable and primarily does not classify people as frail or non-frail but rather assigns a score based on health status. However, Rockwood *et al*. proposed FI cut-off points to define phenotypical population subgroups with increasing levels of frailty. For example, in one of their studies they proposed FI ≤ 0.08 as 'non-frail', FI ≥ 0.25 as 'frail', and the rest as 'pre-frail'.[21] In another of their studies, they proposed FI ≤ 0.03 as 'relatively

fit', 0.03 < FI ≤ 0.10 as 'less fit', 0.10 < FI ≤ 0.21 as 'least fit', 0.21 < FI ≤ 0.45 as 'frail', and FI ≥ 0.45 as 'most frail'.[22] Age-specific FI cut-offs have also been proposed.[23]

Frailty in Surgery

Surgeons and anaesthetists accept that working with frail patients is a common but challenging scenario.[24] Current surgical decision-making can be subjective ('eyeball'[25]) and often misjudges a patient's physiologic state.[26] As a marker of low physiological reserve and vulnerability, frailty has emerged as an independent predictor of morbidity and mortality after surgery.[27-29] Crucially, frailty improves the predictive power of 'conventional' surgical risk scores.[30-32] To date, frailty tools have been successfully validated (as more accurate approaches to risk stratification) in many types or surgery, including cardiac[32-35], thoracic[36], gastrointestinal[37-40], vascular[41, 42], head and neck[43], kidney transplant[44], and orthopaedic[45]. Objective frailty assessment tools may have implications in preoperative decision making in selecting patients who optimally benefit from surgery[46], and may prove beneficial when weighing the risks and benefits of surgery, allowing objective data to guide surgical decision-making and patient counselling.[47]

Frailty in Oncology

Frailty has also emerged as a potential aid in the *vulnerability assessment* of older patients undergoing oncology (e.g. chemotherapy) treatments. Indeed, a comprehensive geriatric assessment (CGA) approach, which also evaluates elements of frailty, may be of great interest for those oncologists who want to identify older patients likely to develop severe toxicity and severe side effects in response to aggressive treatment.[48, 49] The use of 'frail-friendly' (i.e. less aggressive) chemotherapy regimens (i.e. aimed at control of further disease progression rather than maximum tumour shrinkage) may benefit the more vulnerable patients, lowering their rates of premature withdrawal, complications and early mortality[50], in addition to improving their quality of life. In that light, oncology trials tailored for the elderly or frail are needed[51], and examples of frailty-tailored oncology treatment approaches are already available in lymphoma[52] colorectal cancer[53], and gynaecologic oncology[54].

Frailty as a Framework for re-thinking 'traditional' Medical Risk Factors

In non-frail adults, a substantial body of evidence has provided substantial insight into the epidemiology and risk factors of cardiovascular disease.[55] However, the study of these 'traditional' risk factors in frail populations is providing very interesting paradoxes. For example, recent evidence suggests that hypertension may be *beneficial* in frail people older than 85 years [56]. A study showed that the association between BP and mortality varies by walking speed: among faster walkers, those with elevated systolic BP (>/= 140 mm Hg) had a greater adjusted risk of mortality compared with those without, but among slower walkers, neither

elevated systolic nor diastolic BP (>/= 90 mm Hg) was associated with mortality; in participants who did not complete the walk test, elevated BP was strongly and independently associated with a *lower* risk of death.[57]

Low walking speed, inability to walk, or recurrent falling, can all be markers of frailty and underlying complex systems.[58] Another recent study showed that antihypertensive medications were associated with an *increased* risk of serious fall injuries, particularly among those with previous fall injuries and multiple chronic conditions.[59]

The *Leiden 85-plus study* has shown that a decreasing trend in systolic blood pressure (SBP) between 85 and 90 years is associated with *increased* mortality, and that 90-year-olds with SBP of 150 mmHg or less had *increased* mortality risk, independent of the SBP trend in preceding years.[60] Furthermore, it has been shown that in patients aged 85 or more with impaired cognitive functioning, higher SBP is associated with *reduced* risk of stroke.[61] A careful review of the epidemiology suggests that, in the oldest old, and especially in the frail, hypertension is *not* an attributable risk factor for stroke, and hypercholesterolemia has little effect on stroke risk overall.[62]

Another example in the area of diabetes management are the recently published *evidence-informed guidelines for treating frail older adults with Type 2 Diabetes Mellitus* (T2DM),[63] which recommend more liberalised targets (HbA1c ≥ 8%), treatment simplification, and less monitoring. In patients with long-standing T2DM and at high risk for cardiovascular events, intensive BP control and fibrate therapy in the presence of controlled low-density lipoprotein cholesterol levels did *not* produce a measurable effect on cognitive decline at 40 months of follow-up; furthermore, intensive BP control was associated with greater *decline* in total brain volume at 40 months relative to standard therapy.[64]

Frailty for more Appropriate Prescribing

Frail older people have been grossly underrepresented in clinical trials, and many day-to-day treatment decisions are still based on evidence extrapolated from more robust patient groups with fewer physiological deficits.[65] There is very limited evidence on the safety and efficacy of medicines in older adults, particularly in the frail, who often have multiple co-morbidities and functional impairments.[66] The risk of adverse drug reactions (ADRs) increases with increasing patient frailty, and since all physicians are likely to provide care for this group of vulnerable patients, understanding the concept of frailty may help to optimise medication prescribing for older people. The incorporation of frailty measures into future clinical studies of drug effects and pharmacokinetics is important if we are to improve medication use and guide drug doses for fit and frail older people.[65] Furthermore, individualised prescribing could reduce the risk of adverse drug reactions in at-risk frail older patients.[67] Specific guidelines for the management of common conditions will be developed tailored to the *biological age* or *frailty status* of older persons [68].

Frailty as an Indication for Comprehensive Geriatric Assessment (CGA)

Importantly, the emerging evidence base for the frail is not only about reducing interventions (e.g. saving the patient – and the health care system – from tight blood pressure and glycaemic controls), but also about proactively intervening. The most notable example is the *Cochrane systematic review* on Comprehensive Geriatric Assessment (CGA) for older adults admitted to hospital [69]. This review showed that CGA (a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of a frail elderly person in order to develop a co-ordinated and integrated plan for treatment and long-term follow up) increases a patient's likelihood of being alive and in their own home at up to 12 months [69].

Conclusion

In clinical care provision, frailty assessment tools are likely to help clinicians assess vulnerability in specific clinical scenarios. With high degree of probability, there is presently no other area of Medicine where such an exciting evidence gap has emerged concerning a sizeable and growing sector of the population, with simultaneous potential to improve patient outcomes, reduce healthcare expenditure in ineffective (and potentially harmful) interventions, and help focus resources on new, proactive and effective CGA-based models of specialist care. The frailty paradigm demands an even greater degree of involvement at the individual patient level, and will pave the way towards a much more *personalised medicine* in old age.

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