Frailty Is Not a Fatality

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Key Messages

- Frailty corresponds to an extreme vulnerability to poor resolution of homeostasis after stressors, due to loss of physiological reserve across multiple systems, which causes an increased risk of adverse health-related outcomes.
- The prevalence of frailty is higher in women and increases with age although the signs and symptoms of frailty are not rare in the middle-aged population.
- Frailty is a dynamic process; the recognition and modification of pre-clinical manifestations and modifiable risk factors, also among adults and young individuals is essential.
- Since frailty is a public health priority, its assessment should be integrated into routine clinical practice for older patients, encouraging the early identification of at-risk individuals and subsequent interventions.
- Frailty and pre-frailty are potentially reversible. Solid evidence supports the efficacy of physical exercise. Current evidence supporting nutrition interventions is scare. Multicomponent interventions, after a global geriatric assessment, appears the best way of reversing the frailty process.

6.1 Definition

Frailty is a condition of extreme vulnerability to poor resolution of homeostasis after stressors, due to loss of physiological reserve across multiple systems, which causes an increased risk of adverse health-related outcomes [1, 2]. Frail older adults

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have higher risk of adverse health events, including falls, delirium, disability onset, hospitalization, institutionalization, and death [1–3].

6.2 Frailty Identification and Assessment

Although the definition of frailty is agreed on, there is not currently a universally accepted set of criteria to diagnose frailty. Different models have been developed to operationalize frailty diagnosis in research settings and clinical practice. Among them, the phenotype model [1] and the accumulation of deficits model [4] are those most commonly used. In the Cardiovascular Health Study, Fried validated the frailty phenotype using five criteria: unintentional weight loss, self-reported exhaustion, weak grip strength, slow gait speed, low physical activity. Frailty was defined as a clinical syndrome characterized by the presence of three or more criteria, while pre-frailty was identified by the presence of one or two criteria [1].

At variance, the Frailty Index developed by Rockwood in the Canadian Study of Health and Aging is a mathematical construct to measure the cumulative accumulation of deficits (e.g., symptoms, signs, disabilities, diseases, and laboratory abnormalities) over time [4]. It is calculated as a ratio between the number of deficits observed in the individual divided by the total number of deficit considered. Although originally developed using 92 variables [4], shorter versions of the Frailty Index considering no more than 20 deficits have also been validated [5].

A recent review found 67 different set of criteria to identify frailty [6]. The most common purposes of the instruments were to assess frailty as risk factor for adverse health outcomes (31.3%) and identify risk factor for frailty (22.3%), while few studies used frailty as a guide for clinical decision-making (2.3%) and as a target for intervention (2.3%).

Several instruments demonstrated predictive validity for the risk of adverse health outcomes in different cohorts of older subjects. However, they are built on distinctive concepts of frailty and when compared each other, they identify different older adults as frail [7]. For instance, the FRAIL questionnaire based on five self-reported criteria is suited for clinical screening [8]. The Gérontopôle Frailty Screening Tool (GFST) has been developed to increase awareness of frailty among general practitioners and facilitate screening in primary care [9]. On the other hand, the Frailty index derived from Comprehensive Geriatric Assessment (FI-CGA) is designed for frailty assessment in the clinical setting [10]. Also physical performance measures (e.g., gait speed, the short physical performance battery) have been studied as suitable tools for the assessment of frailty [11]. They are reliable, not time-consuming, objective, and repeatable in the same subject over time and thus they may be easily included in the routine medical examination. In a recent international survey, the most commonly used measure to assess frailty was gait speed test [12].

6.3 Epidemiology

In a systematic review based on 21 cohorts involving 61,500 participants, 10.7% of community-dwelling older persons were identified as frail and another 41.6% as prefrail. However, the prevalence of frailty varies considerably (range 4.0–59.1%) because of different definitions and inclusion criteria adopted among different studies [13]. The prevalence is higher in women and increases with age although the signs and symptoms of frailty are not rare in the middle-aged population [14]. Data from the Survey of Health, Aging and Retirement in Europe (SHARE) showed that among European individuals 50–65 years of age, 4.1% were frail, and 37.4% were prefrail, while in the 65 years and older group 17% were frail and 42.3% prefrail. The frailty criteria more commonly reported in the middle-aged group were exhaustion and low activity, while exhaustion, weakness, slowness, and low activity were frequent in the 65 years and older group [14]. Moreover, frailty is consistently associated with some ethnic groups, e.g., black and Hispanic, living in residential care and lower education and poverty [1, 13–15].

6.4 The Course of Frailty and Its Implications

The pathophysiological pathways underlying the development of frailty are not yet clearly identified. Frailty is the result of an accelerated and cumulative decline across multiple systems (i.e., the skeletal and muscular system, the brain, the immune, inflammatory, and endocrine system). Several theories of frailty have been proposed. Fried et al. conceptualized frailty as a geriatric syndrome, describing a vicious cycle where multiple risk factors and conditions are interacting not only to cause frailty but also to promote its progression [1]. On the other hand, Rockwood et al. proposed a stochastic model where deficit accumulation results from interactions between two processes: on one side, environmental stresses, causing damage, and on the other the systems that control damage and recovery time. The exponential increase in the number of health deficits with age corresponds to the exponential increase of recovery time [16].

In any case, frailty is not a static condition, but instead a dynamic process. In the literature, different studies investigated the natural history of frailty and the determinants of the transition between different stages of frailty over time. In a prospective cohort study of 754 predominantly European American community-living persons, Gill showed that frailty is a dynamic process with frequent transitions between frailty states over time: 57% of participants has at least one transition over 4.5 years. Specifically, transitions to states of greater frailty were more common (43%) than transitions to states of milder frailty (23%), while the probability of transitioning from being frail to nonfrail was very low (0–0.9%) [17]. Rockwood analyzed data for community-dwelling subjects (age 15–102 years at baseline) in the longitudinal component of the National Population Health Survey with seven 2-year cycles to

estimate the outcomes of frailty measured in terms of Frailty Index. In this study, the scale has been divided into different categories: relatively fit (Frailty Index ≤0.03, i.e., no or only one deficit), less fit (0.03 < Frailty Index ≤0.10), least fit (0.10 < Frailty Index ≤0.21), frail (Frailty Index >0.21), and most frail (Frailty Index ≥0.45). At all ages, the 160-month mortality rate was lower among relatively fit people than among those who were frail (e.g., 2% vs. 16% at age 40; 42% vs. 83% at age 75 or older). Moreover, they demonstrated that the relatively fittest people at baseline tended to remain healthy, while the chance of complete recovery declined with age. The chance of staying at the highest level of fitness across all seven cycles declined with age, while the chance of becoming frail increased [3]. In a study of frailty transitions among participants in the San Antonio Longitudinal Study of Aging (SALSA) cohort, diabetes with macrovascular complications, lower education, and longer follow-up intervals were predictors of frailty worsening [18]. Shardell demonstrated that prefrail participants with lower 25-hydroxyvitamin D were 8.9% more likely to die, 3% more likely to transition to frailty, and 7.7% less likely to become robust. On the other hand, transitions from robustness or frailty were not associated with serum 25-hydroxyvitamin D [19]. Lee et al. examined the natural history of transition between frailty states in a cohort of community-living older Chinese people. Among prefrail subjects, a quarter of both genders recovered into the robust state, while 11.1% of men and 6.6% of women worsened into frailty. Moreover, they found significant factors associated with worsening or less improvement in transition between frailty states (older age, history of stroke, lower cognitive functions, diabetes, osteoarthritis, cancer, lung disease, hospitalizations), while higher socioeconomic status was protective [20]. Recently, Pollack and colleagues in a perspective cohort study of 5086 community-dwelling men found that over 4.6 years 35% progressed in frailty status or died, 15% improved, but only 0.5% of them from frail to robust. A comprehensive evaluation of potential determinants of transition in frailty status showed that factors associated with improvement in frailty status included greater leg power, being married, good or excellent self-reported health. On the other hand, any instrumental activity of daily living (IADL) limitations, low albumin levels, high interleukin-6 levels, and presence of chronic obstructive pulmonary disease or diabetes mellitus were associated with lower likelihood of improvement in frailty status [21].

These evidence suggest that frailty is potentially reversible, particularly in the early stages. It would be extremely important to know the life expectancy of older subjects with frailty, but there is currently no study that can provide this information. A better understanding and management of modifiable clinical, social, and functional risk factors may increase the recovery rate of the prefrail individuals or prevent their progression to frailty. Given its multidomain nature, a comprehensive approach is necessary to target frailty and associated factors. Because the improvement in frailty status has been associated with social, functional, and clinical factors, effective strategies may include rehabilitation and interventions that target strength and lower extremity power, social support, nutritional interventions, and improvement management of comorbidity [21].

In the World Report on Ageing and Health published by the World Health Organization, frailty has been considered as a progressive decline in physiological

systems that results in decreased *intrinsic capacity*. The intrinsic capacity is defined as the composite of all the physical and mental (including psychosocial) capacities of an individual. The combination of intrinsic capacity with relevant environmental characteristics and their interactions defines the *functional ability* of the individual. The report defines healthy aging as the process of developing and maintaining the functional ability that enables well-being in older age. Thus, healthy aging reflects the interactions between individuals and the environments, resulting in trajectories of both intrinsic capacity and functional ability [22]. It is noticeable that the prevention of frailty as well as an effective promotion of healthy aging should adopt a life-course perspective. The functional status at older age is the result of behaviors and conditions occurring in the individual during the entire life and the interaction with the environment.

6.5 Interventions

Frailty is a public health priority [23]. Multiple interventions targeting frailty have been investigated. Solid evidence supports the efficacy of exercise in frail older people. A high-intensity progressive resistance training of the hip and knee extensor (chosen because of their importance in functional activities) improved muscle strength and size with associated improvement in mobility and level of physical activity in frail older nursing home residents [24]. Moreover, Gill showed that a program targeting underlying impairments in physical abilities (e.g., balance, muscle strength, ability to transfer from one position to another, and mobility) reduced the progression of functional decline also among physically frail elderly persons living at home [25]. In a more recent trial, the Lifestyle Interventions and Independence for Elders pilot (LIFE-P) study, the incidence of major mobility disability over 2.6 years was reduced in the exercise group compared with a successful aging educational program group. The physical activity program consisted of a combination of walking at moderate intensity, resistance exercises, balance, stretching, and behavioral counseling [26]. Further analyses from the LIFE-P study explored the effects of physical activity on frailty status. Cesari et al. showed that after 12 months of follow-up regular physical activity reduced the frailty prevalence. Moreover, in comparison to successful aging participants, the mean number of frailty criteria in the physical activity group was notably reduced, especially for at-risk individuals (i.e., participants with frailty, and those with multimorbidity) [27]. Exercise has a positive impact on physical determinants and functional outcomes, even if the most effective type and intensity of exercise is uncertain. However, multicomponent training interventions (i.e., focusing on resistance, balance, aerobic, and flexibility training), of long duration ($\geq$5 months), performed three times per week, for 30–45 min per session, generally had superior outcomes than other exercise programs [28].

Although individual nutritional status as well as the dietary style and nutrient intake (e.g., vitamin D) have been demonstrated associated with frailty, current evidence supporting the efficacy of nutritional interventions is scanty [24].

A recent review using the level of frailty as intervention target selected 14 studies designed to prevent or reduce the level of frailty among community-dwelling older adults. The interventions included physical activity, physical activity combined with nutrition or with nutrition and memory training, home modifications, prehabilitation (physical therapy plus exercise plus home modifications), and Comprehensive Geriatric Assessment (CGA). Particularly, the physical activity intervention mostly included strength, balance, coordination, flexibility, and aerobic exercises provided by exercise professionals, with sessions ranging in frequency from once weekly to 5 days per week. Nine of the 14 studies reported that the intervention reduced the level of frailty. On the other hand, studies using Comprehensive Geriatric Assessment had mixed findings [29]. Nevertheless, currently implications of change in frailty level on clinical outcome are not well known. Frost recently evaluated the effectiveness of home- and community-based health promotion interventions on functioning and frailty in individuals with mild or pre-frailty. They identified seven trials: six studies evaluating exercise intervention (single intervention or two intervention, i.e., two exercise interventions or exercise plus nutritions) and one study telemonitoring. Group exercise interventions showed positive effects on functioning, but these were mixed and based on small, low quality studies [30].

In current clinical practice, the gold standard for the management of frailty is the Comprehensive Geriatric Assessment (CGA). The CGA is a multidisciplinary diagnostic process intended to determine a frail elderly person's medical, psychosocial, and functional capabilities and limitations in order to develop a personalized intervention of care and follow-up. This approach is sensitive to detection of levels of frailty [10]. Moreover, this process is closely linked to interventions with subsequent relevant outcomes. Several evidences showed as CGA improves health-related outcomes in frail patients in different setting as hospital [31], home care [32], and nursing home [33].

The relevance of prevention and management of frailty has been recognized by international bodies. The European Commission has recently created the European Scaling-up Strategy in Active and Healthy Ageing including an action group focused on the prevention of frailty and functional (both cognitive and physical) decline [29]. Another relevant European project founded by the Innovative Medicines Initiatives is the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) Study, a large clinical trial specifically designed to implement frailty care and prevention across Europe. In SPRINTT, the efficacy of a multicomponent intervention, based on long-term structured physical activity (including aerobic, strength, flexibility, and balance training), nutritional counseling/dietary intervention, and an information and communication technology intervention, for preventing mobility disability is tested in comparison with a healthy aging lifestyle education program in community-dwelling older persons with physical frailty and sarcopenia [34, 35].

Conclusion

As the world's population ages, the prevention and management of frailty should take on primary relevance. Frailty assessment should be integrated into routine clinical practice for older patients, encouraging the early identification of at-risk

individuals and subsequent interventions. Future studies should focus on trajectories of frailty, and thus on the recognition and modification of pre-clinical manifestations and modifiable risk factors, also among adults and young individuals, evaluating complex multicomponent interventions.

References

1. Fried LP, Tangen CM, Walston J et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146–M156
2. Clegg A, Young J, Iliffe S et al (2013) Frailty in elderly people. Lancet 381:752–762
3. Rockwood K, Song X, Mitnitski A (2011) Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. Can Med Assoc J 183:E487–E494
4. Mitnitski AB, Mogilner AJ, Rockwood K (2001) Accumulation of deficits as a proxy measure of aging. Sci World J 1:323–336
5. Mitnitski AB, Graham JE, Mogilner AJ et al (2002) Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2:1
6. Buta BJ, Walston JD, Godino JG et al (2016) Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev 26:53–61
7. Theou O, Brothers TD, Mitnitski A et al (2013) Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. J Am Geriatr Soc 61:1537–1551
8. Morley JE, Malmstrom TK, Miller DK (2012) A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 16:601–608
9. Cherubini A, Demougeot L, Jentoft AC et al (2015) Relationship between the Gérontopôle Frailty Screening Tool and the frailty phenotype in primary care. Eur Geriatr Med 6:518–522
10. Jones DM, Song X, Rockwood K (2004) Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 52:1929–1933
11. Cerreta F, Ankri J, Bowen D et al (2016) Baseline frailty evaluation in drug development. J Frailty Aging 5:139–140
12. Bruyère O, Buckinx F, Beaudart C et al (2017) How clinical practitioners assess frailty in their daily practice: an international survey. Aging Clin Exp Res 29:905–912
13. Collard RM, Boter H, Schoevers RA et al (2012) Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 60:1487–1492
14. Santos-Eggimann B, Cuénoud P, Spagnoli J et al (2009) Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci 64:675–681
15. Bandeen-Roche K, Seplaki CL, Huang J et al (2015) Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci 70:1427–1434
16. Mitnitski A, Song X, Rockwood K (2013) Assessing biological aging: the origin of deficit accumulation. Biogerontology 14:709–717
17. Gill TM, Gahbauer EA, Allore HG et al (2006) L. Transitions between frailty states among community-living older persons. Arch Intern Med 166:418–423
18. Espinoza SE, Jung I, Hazuda H (2012) Frailty transitions in the San Antonio longitudinal study of aging. J Am Geriatr Soc 60:652–660
19. Shardell M, D'Adamo C, Alley DE et al (2012) Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: the Invecchiare in Chianti Study. J Am Geriatr Soc 60:256–264
20. Lee JSW, Auyeung T-W, Leung J et al (2014) Transitions in frailty states among community-living older adults and their associated factors. J Am Med Dir Assoc 15:281–286

21. Pollack LR, Litwack-Harrison S, Cawthon PM et al (2017) Patterns and predictors of frailty transitions in older men: The osteoporotic fractures in men study. J Am Geriatr Soc 65(11):2473–2479
22. World Health Organization (2015) WHO, Geneva. http://www.who.int/ageing/publications/world-report-2015/en/. Accessed 10 Oct 2017
23. Cesari M, Prince M, Thiyagarajan JA et al (2016) Frailty: an emerging public health priority. J Am Med Dir Assoc 17:188–192
24. Fiatarone MA, O'Neill EF, Ryan ND et al (1994) Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 330:1769–1775
25. Gill TM, Baker DI, Gottschalk M et al (2002) A program to prevent functional decline in physically frail, elderly persons who live at home. N Engl J Med 347:1068–1074
26. Pahor M, Guralnik JM, Ambrosius WT et al (2014) Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA 311:2387–2396
27. Cesari M, Vellas B, Hsu F-C et al (2015) A physical activity intervention to treat the frailty syndrome in older persons—results from the LIFE-P study. J Gerontol A Biol Sci Med Sci 70:216–222
28. Theou O, Stathokostas L, Roland KP et al (2011) The effectiveness of exercise interventions for the management of frailty: a systematic review. J Aging Res 2011:569194
29. Puts MTE, Toubasi S, Andrew MK et al (2017) Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. Age Ageing 46:383–392
30. Frost R, Belk C, Jovicic A et al (2017) Health promotion interventions for community-dwelling older people with mild or pre-frailty: a systematic review and meta-analysis. BMC Geriatr 17:157
31. Ekdahl AW, Sjöstrand F, Ehrenberg A et al (2015) Frailty and comprehensive geriatric assessment organized as CGA-ward or CGA-consult for older adult patients in the acute care setting: a systematic review and meta-analysis. Eur Geriatr Med 6:523–540
32. De Almeida MJ, Hermans K, Audenhove CV et al (2015) Evaluations of home care interventions for frail older persons using the interRAI Home Care Instrument: a systematic review of the literature. J Am Med Dir Assoc 16:173.e1–173.10
33. Mor V, Intrator O, Fries BE et al (1997) Changes in hospitalization associated with introducing the Resident Assessment Instrument. J Am Geriatr Soc 45:1002–1010
34. Marzetti E, Calvani R, Tosato M et al (2017) Physical activity and exercise as countermeasures to physical frailty and sarcopenia. Aging Clin Exp Res 29:35–42
35. Landi F, Cesari M, Calvani R et al (2017) The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res 29:89–100