Editorial

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Facing frailty: Are you ready?

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SUMMARY By far, there is no general consensus concerning the definition of frailty even though it may be a global public health concern with aging of the population. It is regarded as a pathophysiological state before development of a severe illness that is associated with many adverse outcomes. Although previous studies attempted to verify its clinical value to prevent the development of serious illness, robust evidence is lacking. Based on previous studies of frailty, the current study analyzed the problems with existing investigations of frailty and it puts forward future strategies to improve those investigations. Finalizing the definition of frailty is the first step. Next, development of objective tools to identify/measure frailty based on the newest biological and computerized technologies is indispensable. Finally, well-designed clinical trials also need to be conducted to yield compelling evidence regarding the clinical value of medical interventions in frailty.

Keywords frailty, population aging, clinical outcome, rehabilitation, assessment tools

The term "frailty" is often used to describe a decline in one's physical and/or psychosocial state, which is commonly experienced by older adults. However, there is no general consensus concerning the definition of frailty by far. Using this term only for older people is inaccurate. In fact, frailty can develop at any age, and particularly in those who are suffering from chronic illnesses (*1*). Accordingly, frailty can be roughly divided into "aging-related frailty (ARF)" and "non-aging-related frailty (NARF)", such as illness-related frailty. Setting NARF aside, ARF has been highlighted with the rapid increase of the older population. It may be a global public health concern since it will eventually be faced by everyone worldwide. Due to the vague definition of frailty, its precise morbidity, prevalence, and mortality remain unclear. The available data exhibit great heterogeneity among studies. Vetrano *et al*. performed a systematic review and meta-analysis of 48 studies with 78,122 people subjects and found that the prevalence of frailty among people with comorbidities was 16% (95% confidence interval: 12-21%; I^2 = 96.5%) (*2*). In 493,737 participants (37-73 years), Hanlon *et al*. found that approximately 3% were frail, 38% were pre-frail, and 59% were non-frail (*3*). The prevalence of frailty might differ in people with different pathophysiological states (*1*). However, Hoogendijk *et al*. summarized three clinical characteristics of frailty, namely multidimensional, increasing with aging, and dynamic (*1*), which increase the difficulties of settling on an appropriate definition, thereby hampering the formulation of an investigation strategy.

ARF could be a pathophysiological state before development of a severe illness, with involvement of all organs and systems (Figure 1). It could also accompany the development of a certain disease. Undoubtedly, however, ARF is always associated with a battery of adverse outcomes (*4*). The adverse impacts of ARF are multidimensional. It influences both the physiological and psychological state of an individual. It might result in a worse outcome not only for non-communicable diseases but also for communicable diseases. For example, it may increase the risk of falls for patients with neurological deficits; it may induce depression/anxiety in older people with chronic diseases. A notable example of a communicable disease is the COVID-19 pandemic; older people are particularly prone to developing serious illness and suffering from the sequelae of long COVID (*5*). A plausible explanation is that ARF may weaken the immunity of aging people. The complicated interactions among COVID-19 and the other aging-related pathophysiological factors (such as diabetes) finally lead a worse outcome of COVID-19. Hence, ARF is basically a negative impact for older people that might worsen their health, reduce their quality of life (QOL), and enhance the family and social burden they pose. However, whether the frailty eventually develops

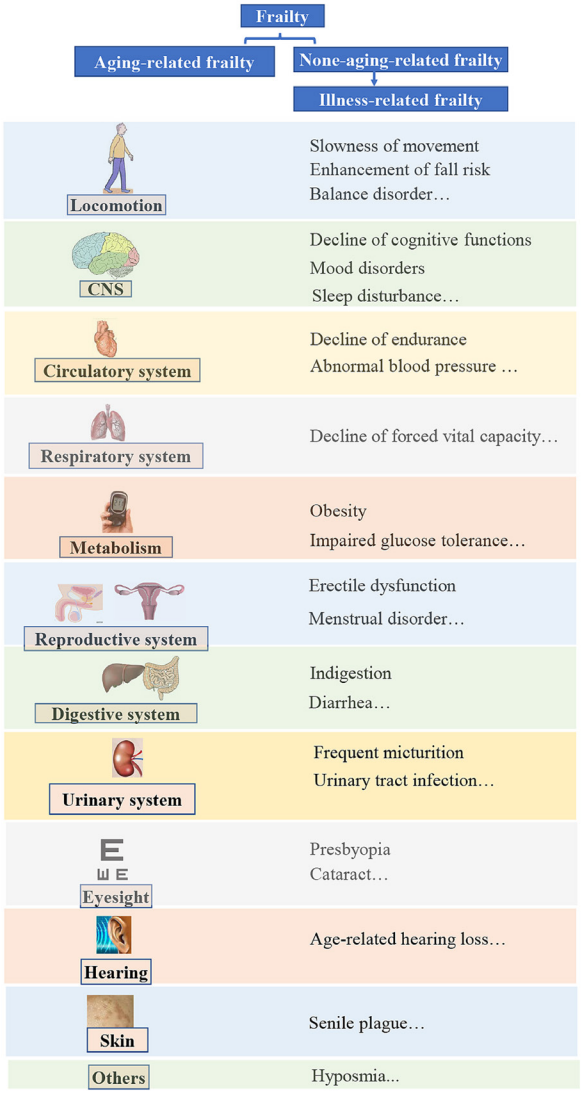

Figure 1. The potential physical changes associated with frailty.

into a serious illness in some cases is uncertain. For example, a recent study by the current author discussed the uncertainty of whether age-related hearing loss can lead to cognitive impairment (*6*).

Alternatively, frailty is a state before a serious illness. Some authors have reported that ARF is potentially reversible (*4,7*). In most cases, ARF is a chronic, progressing, and gradual process. It might serve as an alert for some serious (life-threatening) illnesses. Appropriately identifying ARF and implementing an early medical intervention might help to prevent the development of a serious illness, improve QOL, and reduce the mortality of older people. In this regard, appropriate identification and treatment of ARF are quite important. However, development of satisfactory tools to screen for/confirm ARF remains challenging. In a series of papers published in the Lancet, authors reviewed most of the available tools, including the identification of a frailty phenotype (*8*), and other behavioral instruments (*1,4*). These tools are widely used to estimate the outcomes of a certain medical intervention. However, there is still no compelling evidence to elucidate the value of identifying frailty to improve clinical practice. In addition, most of these instruments are subjective self-reported scales, which might suffer from observation bias. There is no gold standard available for the diagnosis/identification of frailty. Using different frailty tools may yield great variability in certain populations, such as in solid-organ transplant candidates (*9*). Accordingly, highly specific tools to identify frailty in different clinical scenarios are eagerly anticipated. Other than measurements of behavior, more "objective" indices, such as aging biomarkers are highlighted. Recently, Ren *et al.* published their plan to establish an Aging Biomarker Consortium to explore/identify/evaluate aging-related biomarkers at the cellular, organ, and organismal levels so that the aging-related pathological state could be predicted. In their view, all of these "biomarkers" could be objectively measured, and some of those could be identified as "drivers of aging" and could be potentially used as intervention targets for aging. Noteworthily, multi-omics technologies and artificial intelligence (AI) should be used to establish an "aging index", which might often be used in the study of ARF (*10*). Several suggestions for tools to identify ARF are given based on the current author's experience with behavioral tests (*11,12*): *i*) Objective, which means all the behavioral assessments should be done by an objective recorder and can be quantified with a standard algorithm. Technologies like the Kinect sensor might be useful, and robust motor analysis software is indispensable (*13*). *ii*) Specific, which means the tools should be highly specific, particularly suitable for certain domains (cognitive function, motor function, cardiovascular care, *etc*.). ARF is a multidisciplinary problem. Using a general tool such as Fried's phenotype is good for screening, but sometimes it is difficult for a population with different medical goals. Hence, specific tools for different medical goals are anticipated. *iii*) Behavior should be combined with biomarkers. Using the aforementioned "aging index", or developing a comprehensive "frailty index", might be a good approach for precise identification of frailty (Figure 2).

Although intervention in ARF might help to improve the clinical outcomes of older people, robust evidence remains lacking. But from the viewpoint of rehabilitation, using exercise to add physical power and designing a psychological intervention to reduce stress would help to improve the physical state and QOL of an older individual. This viewpoint is in line with some theories in traditional Chinese medicine (治未病, preventive treatment of disease). In this regard, computerized rehabilitation approaches, using technologies such as augmented reality, virtual reality, exoskeleton systems, and robot-assisted rehabilitation, can be an option for older people who have ARF.

As a new medical discipline, investigation of frailty is

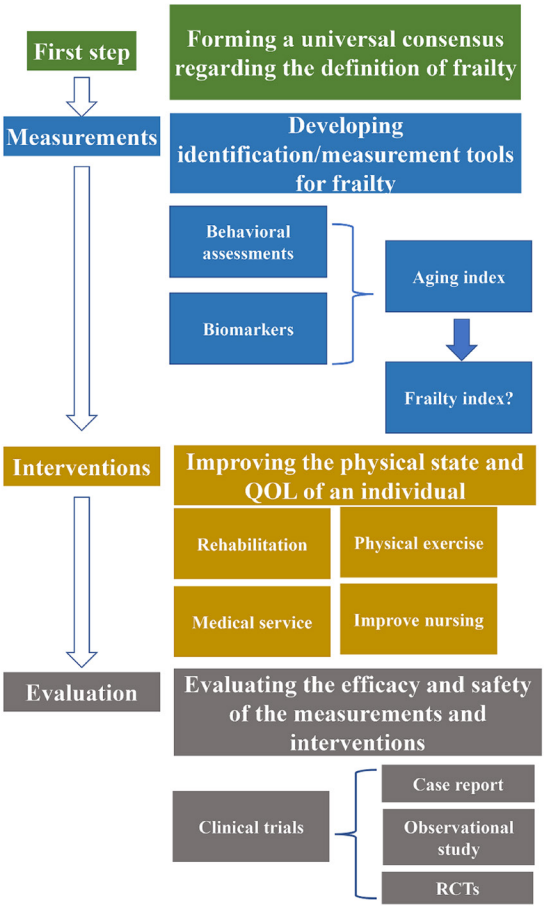

Figure 2. The future strategy to fight against frailty.

not work limited only to the geriatrist. Instead, it should be investigated through multidisciplinary collaboration. Most important is to reach a full consensus regarding the definition of frailty and to develop assessments to identify frailty (Figure 2). Well-designed, large, long-term clinical validation is also anticipated. Indeed, now is the right time to formulate a strategy to fight frailty.

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