Review

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Geriatric syndromes, chronic inflammation, and advances in the management of frailty: A review with new insights

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SUMMARY As people age, geriatric syndromes characterized by frailty significantly impact both clinical practice and public health. Aging weakens people's immune functions, leading to chronic low-grade inflammation that ultimately contributes to the development of frailty. Effectively managing geriatric syndromes and frailty can help alleviate the economic burden of an aging population. This review delves into the intricate relationship among aging, infection-induced inflammation, chronic inflammation, and frailty. In addition, it analyzes various approaches and interventions to address frailty, such as smart rehabilitation programs and stem-cell treatments, offering promising solutions in this new era. Given the importance of this topic, further research into the mechanisms of frailty is crucial. Equally essential is the devising of relevant measures to delay its onset and the formulation of comprehensive clinical, research, and public health strategies to enhance the quality of life for elderly individuals.

Keywords HIV infection, community, multi-dimensional intervention, smart rehabilitation, stem cell treatments

1. Introduction

1.1. Aging and geriatric syndromes

With the improvement of the medical and health care system, human life expectancy has gradually been extended, and life expectancy is increasing worldwide; by 2040, it is expected to further improve and exceed 80 years in most countries (*1*). As of 2019, 88 out of 188 countries have been defined as aging societies, with the proportion of the population aged 65 or older exceeding 7% (*2*). The proportion of the population age 65 ≥ is estimated to increase from 9% in 2019 to 16% by 2050 (*3*). Statistics indicate that the prevalence of aging-related diseases will increase as well. Geriatric diseases such as multiple comorbidities, functional impairment, cognitive impairment, and malnutrition have garnered greater attention. Geriatric medicine has emerged and developed over the years.

Geriatric syndromes (GS) are a concept commonly used in geriatric medicine that refers to syndromes with the same clinical manifestations caused by multiple diseases or multiple factors (including clinical, psychosocial, and environmental vulnerability). Based on a literature review, four shared risk factors – older age, baseline cognitive impairment, baseline functional impairment, and impaired mobility – were identified across five common geriatric syndromes (pressure ulcers, incontinence, falls, functional decline, and delirium) (*4*). Frailty, an important clinical feature of GS, is a prominent problem in aging of the population. At present, the definition of frailty has not been completely standardized. Fried *et al*. proposed that frailty is a clinical syndrome based on studies related to cardiovascular health, in which the reserve and function of several physiological systems are reduced. Those physiological systems are highly correlated with age, resulting in increased physical vulnerability and an increased risk of falls, hospitalization, death, and other adverse consequences. Frailty is believed to be present if the patient experiences three or more of the following: unintentional weight loss, self-reported exhaustion, weakness, a slow walking speed, and little physical activity (*5*). In 2013, a consensus group

consisting of delegates from 6 major international societies conceptualized frailty as "a medical syndrome with multiple causes and contributors, which is characterized by diminished strength, endurance, and reduced physiologic functions that increase individual's vulnerability and dependency, and/or death" (*6*).

1.2. Frailty, geriatric syndromes, and beyond

Although frailty is a main feature of GS, it is not limited to the elderly. Studies have indicated that about 7-20% of the elderly are identified as frail, though it has a similar prevalence among the middle-aged (*5,7*), Due to different concepts, standardization, and study populations, the prevalence of frailty fluctuates widely (between 4-59%) (*8*). Women ages 45-79 have, on average, a higher frailty index and higher prevalence of frailty than men. For every 0.1-increment in the frailty index, adjusted for established and potential risk factors for death, the risk of all-cause death increases (hazard ratio (HR): 1.68, 95% confidence interval (CI): 1.66-1.71). Moreover, this association was stronger in younger people than in older people (*7*). At present, studies have also increasingly indicated that the actual age of the elderly is not sufficient to predict disease prognosis or death, which indicates that the concept of frailty may provide a more objective description of chronic health problems in the elderly and explain the differences in disease prognosis, outcome, and quality of life (*9*). Frailty is an emerging global health burden with significant implications for clinical practice and public health. Frailty is dynamic but also preventable. Strategies to prevent its pathogenesis or slow its progression are of great importance (*8*). The risk factors for developing frailty involve sociodemographic, clinical, lifestyle, psychological, and biological factors (*8,10*). The relationship between chronic inflammation and aging has become the focus of attention.

2. Human immune system and frailty

The human immune system includes innate immunity and adaptive immunity. With age, thymus atrophy, a decrease in naive lymphocytes, and decline of adaptive immune function mainly manifest as follows: impaired antigen presentation, naïve T-cell priming, diminished cluster of differentiation (CD) 8 + T cell cytotoxic function, shrinkage of naïve B-cell and T-cell repertoires, and the production of lower amounts of highly acidity antibodies (*11*). The change in innate immunity differs, and findings have suggested that innate immunity is weakened (*3*). Bleve *et al*. demonstrated that the innate immune cells continue to function relatively well in the elderly (*12*). Innate immunity undergoes more subtle changes that could result in mild hyperactivity (*13*).

In adaptive immunity, adult T cell replenishment relies less on thymic activity and more on homeostatic self-renewal of initial T cells, while the production of nascent T cells is entirely dependent on the thymus. As aging occurs, one of the major changes in adaptive immunity is thymus degeneration, which leads to changes in the number of initial T cells. CD4 T cells can maintain their number through homeostatic proliferation, while CD8 T cells significantly decrease (*14*). In innate immunity, the proportion of macrophages, chemotaxis, antigen-presenting capacity, and phagocytosis capacity all decrease with age (*3*).

2.1. Low-grade chronic inflammation and frailty

However, some signaling pathways are abnormally activated and some cytokine levels (such as IL-6, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and clotting factor) abnormally increase (*15*). Therefore, changes in the innate immune system are paradoxical. On the one hand, as immune function declines, the body continues to produce inflammatory factors in response to intruders. On the other hand, most senescent cells secrete a suite of cytokines, growth factors, and proteases, known as the senescence-associated secretory phenotype (SASP) (*3*). The SASP is a bioactive secretome that promotes the recruitment and activation of immune cells that clear senescent cells when clearance fails. The process results in the accumulation of senescent cells and SASP factors, which eventually contributes to diminished tissue function and steadily elevated proinflammatory tone (*16*). In young healthy tissues, SASP is usually transient and tends to contribute to the preservation or restoration of tissue homeostasis, but inflammatory factors gradually accumulate during aging. SASP is thought to be a driving force behind the low-level, chronic inflammation that causes or exacerbates age-related pathologies (*17*). This particular low-grade chronic inflammatory state is called "inflammation" and is non-infectious inflammation (*15*).

At present, many studies have suggested that chronic low-grade inflammation may be part of the underlying cause of age-related frailty (*18-20*). There are many factors associated with frailty in low-grade chronic inflammation, including IL-6, CRP, TNFα, IL-10, IL-8, IL-9, and MCP-1 (*21*). Research has focused more on IL-6, TNFα, and CRP (*22,23*), and the conclusions are not entirely consistent. A meta-analysis of 4,263 patients from 45 studies by Xu *et al*. suggested that peripheral inflammatory biomarkers, *i.e.*, lymphocytes, IL-6, CRP, and TNF-α, are related to frailty status (*24*). A meta-analysis of more than 20,000 older adults highlighted that frailty and prefrailty status were directly related to inflammatory markers, and especially CRP and IL-6 levels (*25*), which was consistent with Marcos-Perez *et al*. (*26*). A longitudinal study of 981 community-dwelling elderly men found that IL-6 was associated with frailty events, but there was no statistically significant difference between CRP and frailty (*27*). A study of 347 community-dwelling elderly patients found that the level of IL-6 in pre-frail patients was significantly higher than

that in non-frail subjects (*28*). Frai elderly people living in the community have higher levels of TNFα compared to healthy elderly people (*29*). However, Marcos-Perez *et al*. contend that there may be a correlation between TNF-α and frailty that is significantly weaker than the correlation between CRP and IL6 (*26*). In addition, the relationship between inflammatory factors and frailty also differs in elderly patients of different ages. An analysis of 80 studies (58 on frailty and 22 on sarcopenia) by Picca *et al*. found that IL6 was only related to frailty in people < 75 years (*29*).

A meta-analysis by Byrne *et al*. suggested that intervention trials in frail and sarcopenic older adults could also reduce CRP, IL-6, and TNF-α, but there was a lack of literature consistency (*30*). The pan-immune inflammation value (PIV) has also received attention. By calculating the PIV ((neutrophils × monocytes × platelets)/lymphocytes) in 405 elderly patients, Okyar Bas *et al*. concluded that both PIV and PIV-high (> 372) were significantly associated with frailty independently of confounders (*31*). In conclusion, CRP, IL-6, and TNF-α can be used as indicators to evaluate effectiveness in the process of frailty assessment, prediction, and intervention, and IL-6 may be of greater significance.

2.2. HIV infection and frailty

External infection is one of the factors for frailty. Human immunodeficiency virus (HIV) infection accelerates aging and can induce frailty. Illnesses that are attributes of the elderly are highly frequent among people infected with HIV. However, they develop at a much earlier age (10-15 years earlier), and even more so in patients treated with highly active antiretroviral therapy (HAART) patients (*32,33*). Geriatric HIV is defined as people 50 years of age or older who are infected (*34,35*). Frailty studies in patients with acquired immune deficiency syndrome (AIDS) caused by HIV infection suggested that patients with HIV/ARDS are more likely to suffer from frailty (*36*). The Multicenter AIDS Cohort Study (MACS) indicated that HIV infection increases the likelihood and timing of a frailty-related phenotype compared to HIV-uninfected controls (*37*). Immune damage caused by HIV is characterized by the destruction of CD4 +T cells. As the number of CD4 +T cells in patients' peripheral blood decreases, HIV-related complications and mortality also increase (*38*). Therefore, abnormal immune function after infections is considered to be one of the causes of frailty, which has led to an exploration of the relationship between immune aging and frailty in the non-HIV/ARDS population.

According to one study, out of a total of 566 older patients from eastern China age 50 or older, viral suppression was observed in 446 (78.8%), treatment was immunologically effective in 410 (72.4%), and treatment was effective in 324 (57.2%) (*39*). As reported, geriatric HIV rapidly increases after HAART treatment. Data indicate that the proportion of patients age 60 and older who were newly diagnosed with HIV in China increased from 12% to 25% from 2011 to 2019 (*39, 40*). In patients with HIV, and especially geriatric HIV patients, frailty is the main cause threatening their life. Like in older adults without HIV, these HIV cohort studies have indicated an increased frailty burden with age, among women, and with increased chronic comorbidities (*41-43*).

The higher prevalence of frailty may have multiple factors, including direct HIV infection, suboptimal medication after infection, early control of infection, or comorbidities (either infectious or non-infectious) (*44-46*). HIV infection is a type of systemic disease. Sustained activation of the immune system and the chronic inflammatory reaction after its attack are important factors for the early onset of frailty (*47, 48*). Compared to HIV+ non-frail men, HIV+ frail men had higher levels of the serum inflammatory markers sCD14, sIL2Rα, sTNF-R2, IL-6, TNF-α, and CRP (after adjusting for multiple comparisons, age, race, study site, and education) (*49*).

In conclusion, the number of elderly patients and geriatric HIV patients will continue to rapidly increase, and the relationship between chronic inflammation and frailty warrants more attention.

3. Assessment and management of frailty

Frailty is a multidimensional and dynamic spectrum syndrome. Here, a series of specific tools targeting frailty triggered by chronic inflammation in the elderly are proposed and discussed. Elderly who become frailty are vulnerable to many medical conditions, including cardiovascular diseases and dementia. There are generally three stages (physical outcomes) of frailty: falls, hospitalizations, and death (*50*). However, frailty may be dynamic, which means there are often transitions between stages including not frail, pre-fail, and frail (*50*). This variation should be considered when considering backup management plans to avoid potential risks if frailty worsens.

3.1. Frailty screening and post-screening assessments

The screening process is the first step in considering management options in most cases with a massive population. Popular validated screening instruments include the Clinical Frailty Scale, FRAIL Scale, Cardiovascular Health Study Measure, and K-FRAIL scale (*6*). These scales are simple and can be used under most conditions. They mostly focus on clinical judgments of physical condition and rely on self-reported questionnaires. Early screening of at-risk populations for frailty is recommended. After preliminary screening, professionals should determine whether a "pipeline" for CGA and related tools is appropriate for implementation for the people being tested. The frailty assessment

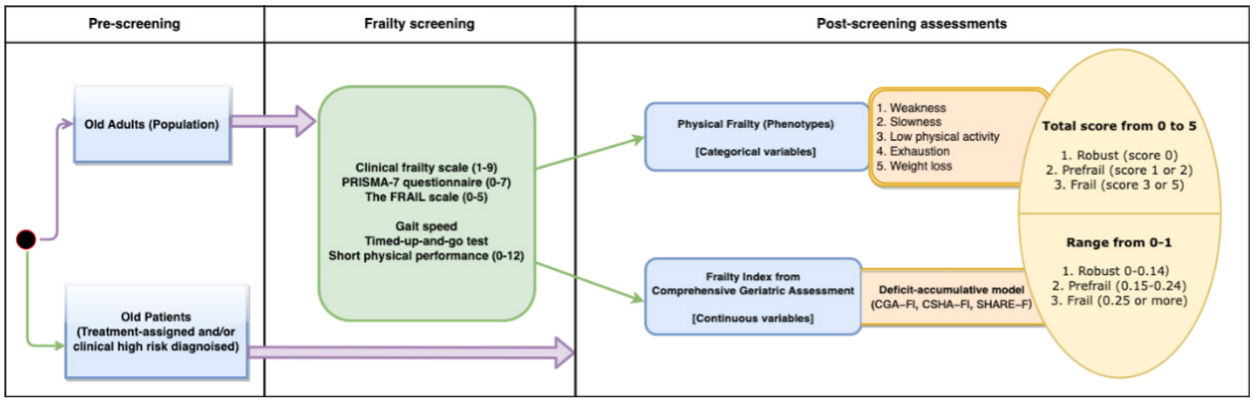

Figure 1. A flow diagram of the frailty assessment process.

process is shown in Figure 1.

There are two well-validated post-screening methods of assessing frailty: 1) the phenotypic definition of frailty and 2) the accumulation of deficits definition of frailty. The phenotype definition sticks with biological concepts, considering frailty to be losing physiological reserve (*5*). Frailty is considered if the patient meets 3 out of the 5 indicators among 1) weakness (grip strength), 2) slowness (gait speed deviation), 3) exhaustion (self-reported fatigue questionnaire), 4) activity decline (energy expenditure from questionnaire-based calculations), and 5) unintentional weight loss. The accumulation of deficits definition relies on index numbers mapped by healthcare data and self-reported items (*51*). At most, at least 30-40 measurements have to be taken, so this assessment is comparatively time-consuming. Although there is no gold standard for frailty assessment, FI is more feasible for proposing follow-up management because it interprets frailty as a spectrum of aging, which is closer to its dynamic nature. Therefore, this model will be more feasible for the identification of highly vulnerable patients while figuring out the physiological risk domains. Its quantitative nature is more systematically beneficial for assessing frailty causally linked to chronic inflammation.

By now, the medical community has reached a consensus in consulting the guidelines published by the task force of the International Conference on Frailty and Sarcopenia Research in 2019 (*52*). Strong recommendations proposed include 1) a multicomponent physical activity program, 2) a progressive resistance training component, 3) a care plan addressing polypharmacy, management of sarcopenia, weight loss, and causes of fatigue, and 4) a proper plan of social support (*52*). Several consensus-based recommendations should also be emphasized: 1) Cognitive therapy is not systematically recommended, 2) Vitamin D supplementation should be assigned only if it is deficient, and 3) Hormone therapy is not recommended (*52*). These clinical suggestions are vital in an emergency or if the patient is in severely poor health. Routinely implementing and periodically reviewing the treatment plan is recommended.

Management is not only to ameliorate the patient's health but should also focus on formulating and implementing health care plans. The Palliative and Therapeutic Harmonization (PATH) model is a system that can be applied to this process (*53*). It constructs a decision-making system based on the frailty score and dementia stage of the dataset's comprehensive medical history and incorporates medical or surgical interventions. As the frailty level increases, less aggressive treatments will be chosen, which largely adhere to the patients' potential well-being.

3.2. Interventions and training strategies

Frailty is noted to be prevalent in community-dwelling elderly at present (*54*). Infectious diseases are among the leading critical factors for chronic inflammation and frailty (*55*). Accordingly, different training interventions have been proposed to reduce the development of frailty. The physical activity prescription by the American College of Sports Medicine guidelines for older adults emphasizes strength and balance (*56*). There are four ongoing treatments to manage frailty: exercise, caloric and protein support, vitamin D, and reduction of polypharmacy (which is likely to cause adverse reactions that induce pathogenesis). The consensus recommendation that vitamin D is not universally needed should be reviewed, but the three other components can be applied appropriately in different combinations. Patients' diets and quality may contribute to inflammatory factors and lead to frailty. Supply of antioxidant nutrients is feasible. Oral health, gut microbiome health, and metabolome may be future research targets to explore better nutrient management plans (*57*). Studies have indicated that frailty was successfully ameliorated after a combination of nutritional education and a systematic physical training plan (*58-60*). Such a multi-component program is promising and remains the best treatment option.

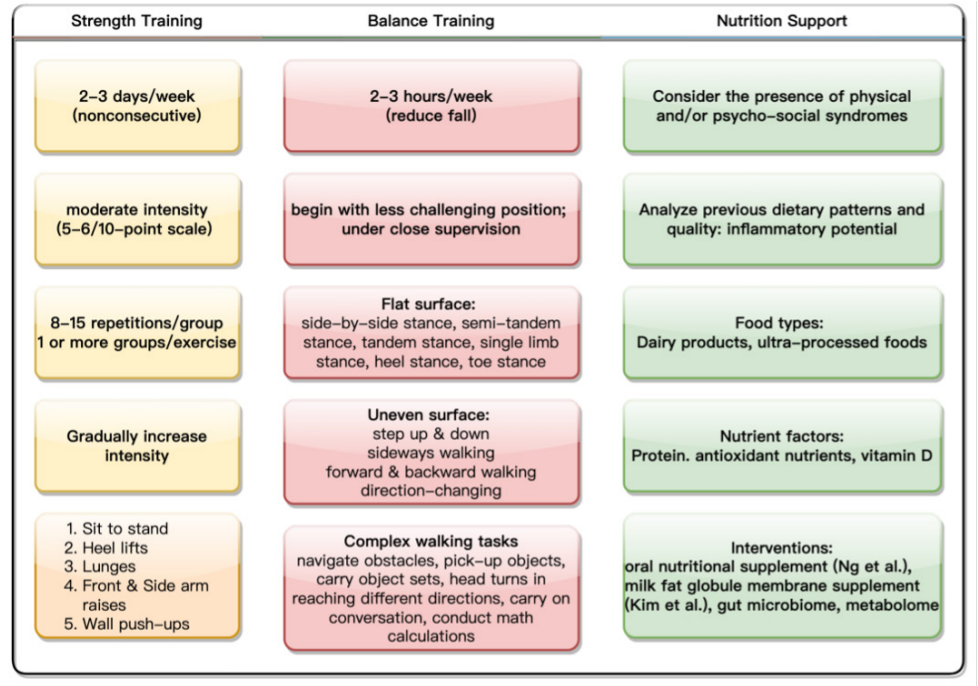

Figure 2. Elements of strength training, balance training, and nutrition support.

Specific prescription plans are outlined in Figure 2 (*61,62*).

However, more research and clinical controlled trials need to be conducted to verify its efficacy and consistency in treating frailty. An optimal set of strategies should be formulated as soon as possible (*63*).

3.3. Smart rehabilitation strategies

With breakthroughs in artificial intelligence, virtual reality, and various computer-programmed systems, smart rehabilitation is an area that should be emphasized. An immersive motor protocol integrated with innovative virtual reality programs was proposed by Pedroli *et al*. in 2019 (*64*). The training program is conducted inside a special room-sized environment named the Cave Automatic Virtual Environment (CAVE). The functional system integrates 3D full-view projectors in combination, a cyclo ergometer, CAVE goggles, stationary bike, and software development tool kit (SDK) inside a PC. Completely virtual training and virtual reality training are two methods of smart rehabilitation (Figure 3).

The exercise designed by Pedroli *et al*. has two main components serving as balance training tasks: "stationary bike riding" and "avoiding the rocks," where a virtual map with obstacles is simulated for patients to exercise. The virtual model models the path of the patient to detect collisions and track his performance. Optimally, this training program can be applied in a lot of different settings, including rehabilitation centers, hospitals, and homes. The virtual environment ensures a safer location for exercise, and many more circumstances can be simulated than a single space of limited size in the real

Figure 3. A conceptual graph of virtual training.

world. Devices such as balance pads, proprioceptive footboards, and rocking footboards can also be used to promote the efficacy of balance training. A tablet-based system has been found to be safer than head-mounted displays and will exploit the potential of 360◦videos at home. In short, high-end settings, low-end technology (higher cost performance), fewer injuries, and portability are the areas for improvement in the future.

3.4. Stem cell treatments

Chronic inflammation is an important mechanism of frailty. Physiological evidence supports this claim and provides new insights into potential treatments. Mesenchymal stem cells (MSCs) were originally isolated from bone marrow in 1968 (*65*). MSCs are plastic-adherent and can differentiate into multiple lineages according to *in vitro* experiments (*66*). MSCs can be

obtained from tissue such as cord blood, adipose tissue, marrow, and bone marrow spaces of long bone, muscles, and peripheral blood (*67-72*). MSCs can exhibit both immunomodulatory and immunosuppressive activity. By interacting with cells from the adaptive and innate immune systems, they can suppress the release of pro-inflammatory cytokines. They also secrete a variety of trophic factors including growth factors, morphogens, chemokines, cytokines, and extracellular vesicles that facilitate an anti-inflammatory response and promote tissue repair (*73-75*). Therefore, this characteristic of MSCs means that they are a type of biological treatment that ameliorates or reverses frailty (*76, 77*).

Clinical trials have revealed that frail patients treated with MSCs had marked improvement in physical performance measures and inflammatory biomarkers, providing new treatment ideas for frailty. In the CRATUS trial, a Phase I study revealed that intravenous, allogeneic, bone marrow-derived mesenchymal stem cell (allo-hMSC)-based therapy is safe and immunologically tolerated in patients with aging frailty (n = 15 mean age 78.4 ± 4.7). The TNF-α level was found to decrease with allo-hMSC treatment, and no significant changes were seen in IL-6 or CRP (*78*). In the Phase II study, (randomized, double-blinded, and dose-finding), 30 patients (mean age 75.5 ± 7.3) diagnosed with frailty received intravenous allo-hMSCs (100 or 200-million [M]) or a placebo. Results indicated that results on the 6-minute walk test, short physical performance exam, forced expiratory volume (in 1 second), and responses on the female sexual quality of life questionnaire all improved, while the serum TNF-α level decreased in the 100 M group compared to that in the 200 M and placebo groups (*77*). These clinical trials suggest that MSC treatment is safe and immunologically tolerated. No trial-related adverse events in participants were identified for 12 months after infusion, (*77, 78*). However, the CRATUS trial was limited due to its small sample size.

Another clinical trial involving 150 subjects with frailty is nearing conclusion. It evaluated the efficacy of Lomecel-B (an allogeneic medicinal signaling cell formulation) in older adults with frailty. The primary endpoint is a change in results on the 6-minute walk test compared to the placebo 180 days post-infusion while the secondary endpoints include changes in other physical function measures and an inflammatory biomarker panel (*79*). A few clinical trials of MSCs in the treatment of frailty are underway, and hopes are to see positive results.

4. Conclusion

Society is facing the worsening problem of aging, and frailty is a key aspect. As effective responses and more comprehensive indicators have been developed, adverse health outcomes of frailty are being ameliorated, yet more challenges in the context of individual pathogenesis and management still need to be addressed. Infection and non-infection inflammation can both induce the pathogenesis of frailty syndromes, and they are more prevalent in vulnerable elderly. Atypical presentations of infections and under-diagnosis or over-diagnosis of different types of infections are common in older adults, requiring multi-component interventions in a multidisciplinary approach for treatment. Systematic and sensitive screening and assessment are important for individuals with infections like HIV.

CGA is considered to be a useful diagnostic process with which to comprehensively assess frailty status and various GS. CGA-based interventions, multicomponent physical training, and multidimensional interventions including stem cell treatments and nutritional support, along with improved communication and collaboration between healthcare sectors, have been found to be effective in hospital, community, and primary care settings. However, caution must be exercised when assessing frailty in general clinical settings. Continuous management systems beyond a simple one-time evaluation should be created.

At the individual level, the management of frailty is a complex issue that requires tailored interventions to preserve the physical function, independence, and cognition of the elderly. At present, there is a lack of quality cutting-edge evidence regarding "how best to identify and treat people with frailty" and "what are the most cost-effective interventions." The challenges of managing frailty, such as the complexity of combined interventions, limited cost-effectiveness, and the need for a simple, low-cost strategy still need to be solved.

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