Research Progress in Clinical Diagnostics and Interventions for Frailty

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Abstract: A cluster of symptoms, including falls, disability, cognitive impairment, decreased autonomic activity, unintentional weight loss and fatigue, are common in older people. This “core symptom complex” defines frailty. Frailty is often related to malnutrition, but is distinguished with the presence of sarcopenia. Frailty embodies a decline in a patient’s overall function, which is not entirely explained by a loss of skeletal muscle mass or decreases in muscle function. Frailty occurs when the individual’s physiological reserve decreases in conjunction with internal dynamic balance disorders and physiological debility. Frailty is associated with adverse clinical outcomes including an increased risk of complications of other conditions and surgery, unintentional injury (falls and fractures), disability, a poor quality of life, and even death. Frailty is common not only in the elderly, but also in patients with cancer, cardiovascular diseases, respiratory diseases, and malnutrition. The prevalence of frailty has been reported to be between 4.0%-59.1% in different reports, and increases with age. Frailty can be diagnosed by the presence of the core symptom complex (frailty phenotype) or based on the frailty index. Early assessment and treatment can significantly improve the health prognosis of patients. Treatments aimed at maintaining an individual’s homeostasis can be more beneficial for preventing or resolving frailty than specifically treating any underlying disease(s). Improving the patient’s nutritional status, implementing physical exercise, and developing individualized multidisciplinary interventions may be the best ways to prevent adverse clinical outcomes in patients with frailty. This article reviews the definitions, diagnosis, epidemiology, etiology and pathogenesis of frailty, as well as the interventions that can be used to combat frailty.

Key words: Frailty; Malnutrition; Clinical outcome; Disability; Quality of life

Introduction

Frailty is an accumulation of deficits including a high possibility of falls, disability, cognitive impairment, reduced voluntary activity, and fatigue, usually unrelated to a specific disease state. Frailty is common in older people but the condition may be underestimated and underdiagnosed. It has been suggested that 25%-50% percent of people aged ≥ 85 years would be diagnosed as experiencing frailty [1,2]. In 2015, the European Society for Clinical Nutrition and Metabolism (ESPEN) Consensus Statement provided a conceptual tree for nutritional disorders, in which it stated that frailty was one of the manifestations of malnutrition, and distinguished with pure-starvation, disease-related malnutrition (cachexia) and sarcopenia [3]. The introduction of the concept of frailty allows for a more accurate and objective reflection of the chronic health problems and medical needs of the population, and can be used to predict the risks of disability, unintentional injuries (such as falls or fractures), the disease prognosis, quality of life and even the likelihood of death. Understanding the pathophysiological changes related to frailty and early detection of the condition are of great significance for reducing the morbidity, disability and mortality of frail people, and may improve their quality of life and longevity.

The Definition and Diagnosis of Frailty

So far there is no standard or uniform definition for frailty. In 2013, the American Geriatrics Society (AGS) describes frailty as ‘a state of increased vulnerability to poor resolution of homeostasis following a stress, which increases the risk of adverse outcomes including falls, delirium and disability’ [4]. The core is disordered homeostasis and increased physiological debt, so that even small external stress can lead to an increased risk of a series of adverse events, including the need for long-term care and even death. General fatigue, weakness and emaciation also fall into the category of frailty syndrome.

In clinical practice, frailty is usually characterized by the following: ① increased risk of falls: a slow gait speed and decrease in body balance are core features of frailty, which greatly increase the risk of falls; ② neuropsychiatric disorders: patients with frailty may appear delirious, show a cognitive decline and/or experience disorders of consciousness; ③ physical disability: frail patients have difficulties in daily self-care and independent living, and are more likely to need others or equipment-based assistance; ④ nonspecific manifestations: including fatigue, unconscious weight loss, and repeated infections.

In the late 1960s, O’Brien TD et al. were the first to
describe frailty as the body’s disproportionate response to adverse events based on a cross-sectional survey of the elderly in the community [5]. Later, frailty was gradually used to classify the health status of the elderly population, and a large number of theoretical models, definitions and diagnoses related to frailty have been reported. There are two diagnostic paradigms that are most widely accepted, the frailty phenotype (FP) and the frailty index (FI).

**Frailty phenotype**

The frailty phenotype is also known as the Fried phenotype, because it was first described by Fried LP et al. in 2001 [1]. Based on data from the Cardiovascular Health Study (CHS), Fried and colleagues developed an operationalized phenotype of frailty in older adults [1]. The FP diagnosis takes physical frailty as the core syndrome, and uses it as a diagnostic standard for frailty. In 2013, Clegg A et al. reported five phenotype model indicators for the FP-based diagnosis, which included weight loss, weak grip strength, slower gait speed, self-reported exhaustion and low energy expenditure [4]. Patients who meet three of the five frailty indicators were diagnosed as experiencing frailty, and meeting one or two of the frailty indicators indicates pre-frailty or intermediate frailty (Table 1).

### Table 1 The five phenotype model indicators of frailty and their associated measures [1].

<table>
<thead>
<tr>
<th>Frailty indicator</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>Self-reported weight loss of more than 10 pounds or recorded weight loss of ≥ 5% per annum</td>
</tr>
<tr>
<td>Self-reported exhaustion</td>
<td>Self-reported exhaustion on the CES-D depression score (3-4 days per week or most of the time)</td>
</tr>
<tr>
<td>Low energy expenditure</td>
<td>Energy expenditure &lt; 383 kcal/week (males) or &lt; 270 kcal/week (females)</td>
</tr>
<tr>
<td>Slow gait speed</td>
<td>Based on standardized cut-off times to walk 15 feet, stratified for sex and height</td>
</tr>
<tr>
<td>Weak grip strength</td>
<td>Grip strength, stratified by sex and BMI</td>
</tr>
</tbody>
</table>

CES-D, Center for Epidemiological Studies-Depression; BMI, body mass index. See the appendix at the end of the article.

Rothman MD et al. undertook a prospective cohort study involving 754 initially nondisabled, community-living persons aged 70 years and older. All the older persons were assessed for seven potential frailty criteria (slow gait speed, low physical activity, weight loss, exhaustion, weakness, cognitive impairment, and depressive symptoms) at baseline and every 18 months for 72 months. The data showed that three criteria (weight loss, slow gait speed and low physical activity) were independently associated with chronic disability, long-term nursing home (NH) stays and death [6]. A slow gait speed was the strongest predictor of physical disability (Hazard Ratio, HR = 3.0, 95% CI = 2.3-3.8), long-term NH stays (HR = 3.9, 95% CI = 2.2-6.7), and was the only significant predictor of injurious falls (HR = 2.19, 95% CI = 1.33-3.60). Reduced physical activity was the strongest predictor of mortality (HR = 2.2, 95% CI = 1.6-3.1). Studies have confirmed that this definition and diagnostic criteria for the frailty phenotype are also applicable for inpatients. The frailty phenotype is also an independent predictor of the surgical outcomes in older patients, including postoperative complications, length of hospital stay and discharge to a skilled or assisted-living facility after previously living at home [7].

**The Frailty index (FI)**

Some researchers believed that in addition to physical factors, indicators of the health and function of the elderly, including mental, psychological and social factors, should also be considered. When the accumulation of negative factors far exceeds the positive factors, frailty occurs. Based on data from the Canadian Study of Health and Aging, Rockwood K et al. developed a dynamic model with deficit accumulation for the classification of frailty. Ninety-two baseline parameters of symptoms (e.g. low mood), signs (e.g. tremor) and abnormal laboratory values, as well as disease states and disabilities (collectively referred to as deficits), were used to define frailty [8]. The FI was calculated based on the presence or absence of each variable as a proportion of the total.

At present, there is no unified standard for the number of FI variables, which typically ranges from 30-70. For example, the Rockwood Frailty Index [8] includes 70 variables, while the Searle frailty index [9] includes 40 variables. The Comprehensive Geriatric Assessment (CGA) includes a total of 60 variables. If a participant has 12 deficits, the FI score was calculated as: the number of variables/the total number of variables (i.e., 12/60 = 0.2). Generally, a FI ≥ 0.25 is considered to indicate that the patient is frail, a FI: 0.12-0.25 indicates pre-frail, and a FI < 0.12 indicates that the patient is still robust [8, 10]. The higher the FI score, the worse the frailty. The FI is a cumulative index, which has the advantage of providing a comprehensive assessment and allows adverse outcomes to be defined more precisely. The FI requires additional clinical translation, as the assessed variables are mostly based on the patient’s medical history rather than any physical measurements. The FI is more suitable for assessing the risk of adverse outcomes, including mortality, by using electronic medical records. Further, it may lead to the proposal of an individualized decision support system based on machine learning methods to create new tools to recognize frailty.

Other definitions or criteria for frailty include: the Clinical Frailty Scale (CFS) [11], Strawbridge Questionnaire [12], Edmonton Frail Scale (EFS) [13], Groningen Frailty Indicator (GFI) and G8 Questionnaire [14], among others.
In addition, Japan [15], South Korea [16,17] and other Asian countries have developed and proposed approaches for frailty assessment based on their own population characteristics. So far, more than 20 different frailty assessment tools have been invented and used in different populations around the world. No frailty assessment tool has been accepted worldwide, so there is an urgent need to create and validate a frailty assessment scale that is applicable for the Chinese population.

**Epidemiology of Frailty**

Due to the different definitions and diagnostic standards used, the prevalence of frailty reported in various studies varies greatly. The overall trends are that the prevalence increases with age and is higher in females than in males [18-20]. A meta-analysis that included data from 21 cohort studies involving 61,500 community elderly population showed a wide range of prevalence rates ranging from 4.0% to 59.1% [21]. In studies using the phenotypic definition, the mean prevalence of frailty was 9.9% (95% CI = 9.6%-10.2%) and the prevalence of pre-frailty was 44.2% (95% CI = 44.2%-44.7%). Eleven of the studies showed a higher prevalence in women than men (9.6% vs 5.2%). The prevalence increased gradually with age, and was 4.0% in those 65-69 years old, 7.0% in those 70%-74, 9.0% in those 75-79, 16.0% in those 80-84 years, and 26.0% in those 85 years and older [21]. Liu ZY et al. [22] conducted a cross-sectional study and analysis of the prevalence of frailty among the elderly in 31 towns of Jiangsu Province in China. A total of 1,773 elderly aged 70 to 84 years old were included (825 males and 948 females). A frailty index (FI) including 45 health variables was used for the diagnosis, which included symptoms, daily activities, diseases, and cognitive and psychological functions. The results showed that the mean FI was 0.14 for males and 0.19 for females. According to the diagnostic criteria (frailty indicated by a FI ≥ 0.25), the frailty rate was 8.2% in men and 23.2% in women. Studies have shown that old age, being an ethnic minority, having a low education level, depression, smoking, multiple comorbidities and anorexia are all risk factors for frailty [23-25]. These factors either independently or synergistically affect the occurrence and development of frailty.

Compared with community-living individuals, residents of health care or long-term care facilities have a higher prevalence of frailty. A cross-sectional study in the Netherlands showed that all elderly patients admitted to the geriatric department were frail, while the prevalence of frailty in other wards was 50%-80% [26,27]. A European multi-center study showed that 48.5% of 307 patients with acute non-ST-segment-elevation myocardial infarction (non-STEMI) had frailty, 24.1% of whom had moderate-to-severe frailty [28]. After reanalyzing data from a multi-center cohort study of Chinese cancer patients (INSCOC study) [29], Jin X and colleagues reported that the overall prevalence of frailty was 55.2% (a total of 2,959 cancer patients) [30]. Atakul E et al. similarly showed that 42.2% of patients receiving treatment for hematological malignancy had moderate to severe frailty [31]. A meta-analysis involving 2,915 cancer patients in 20 studies showed that the prevalence rates of frailty and pre-frailty were 42% and 43%, respectively [32]. However, the prevalence rate of frailty in the ICU was higher, up to > 80% [33].

**Adverse Clinical Outcomes of Frailty**

Frailty is associated with adverse clinical outcomes, including more complications, more hospitalizations and a longer total length of stay, more medical care and even a greater risk of death. Gill TM et al. [34] conducted a 10-year prospective cohort study of elderly people (n = 754) from different regions. At the beginning of the study, subjects had normal autonomous activities and no functional disorders, and a comprehensive assessment was conducted every 18 months for 72 months. Data were analyzed for all deaths (a total of 383) which were classified as being due to cancer, dementia, organ failure, frailty, acute death, and ‘others’. The results showed that among all causes of death, frailty accounted for the highest proportion (27.9%, n = 107), followed by organ failure (21.4%) and cancer (19.3%).

Many researchers have reported the incidence of frailty in patients with cancer, cardiovascular disease, respiratory disease, and surgery, and have described its impact on clinical outcomes. A prospective cohort study of bladder cancer patients undergoing radical cystectomy showed that preoperative moderate to severe frailty increased the risk of postoperative complications within 30 days and within 90 days, with odds ratio, OR values of 4.87 (within 30 days) and 3.01 (within 90 days), respectively [35]. Moderate to severe frailty also significantly increased the risk of an Eastern Cooperative Oncology Group performance status (ECOG) score ≥ 3 (moderate frailty: OR = 45.00, 95%CI = 6.92-437.69, P = 0.0010; severe frailty: OR = 17.85, 95%CI = 3.21-143.26, P = 0.0079) [35]. A meta-analysis of the correlation of frailty with the postoperative outcomes in individuals aged 65 years and over undergoing elective surgery for colorectal cancer was performed that involved four studies and 486 participants in total. Regardless of the definitions of frailty and postoperative outcomes, the frail patients had less favorable outcomes in all of the studies, including a higher risk of developing moderate to severe postoperative complications, longer hospital stay, higher readmission rate, and a lower long-term survival rate [36]. A 4-year prospective cohort study for older breast cancer patients showed that patients identified as pre-frail/frail had a significantly worse long-term health-related quality of life (HRQOL) compared to robust patients, in terms of their physical function, social roles, fatigue, depression and incidence of sleep disorders at follow-up [37].

In recent years, frailty has become a key concern in patients with cardiovascular disease (CVD). Numerous
factors affecting the prognosis of elderly patients with cardiovascular disease, such as frailty, disability and cognitive dysfunction, have been paid more attention by cardiologists and geriatricians. The reported prevalence of frailty ranges from 10% to 60%, depending on the CVD burden, as well as the tool and cut-off chosen to define frailty. Epidemiological studies have confirmed that in patients with stable CVD, acute coronary syndromes, heart failure, and surgical and transcatheter interventions, frailty caries a relative risk of >2 for mortality and morbidity after adjusting for age and comorbidities [38]. Frailty is also a strong independent predictor of increased emergency department visits and hospitalizations in a community cohort of patients with heart failure [39]. Therefore, an assessment of frailty may provide additional valuable prognostic information to help clinicians choose better treatments for patients, building on existing models of cardiovascular disease risk. The American Heart Association and the Society of Geriatric Cardiology released a scientific statement in 2007 to emphasize that assessments of frailty, co-morbidity, and functional status are important in the treatment of elderly patients with non-ST-segment elevation myocardial infarction [40]. The Journal of the American College of Cardiology (JACC) also used the phrase “high-priority theme in cardiovascular medicine” to describe the role of frailty in cardiovascular diseases in 2014 [38].

Etiology and Characteristic Related Frailty

Frailty is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stress. When a frail individual’s physiological reserve is reduced to a certain level (close to a threshold), the internal dynamic balance is disturbed, the integrity of health and function is impaired, increasing their vulnerability to stress, resulting in adverse clinical outcomes. Frailty can be divided into primary and secondary disease. Primary frailty is when the occurrence of frailty is not directly related to a specific disease(s), and is mainly the result of physiological aging of the organism. Secondary frailty refers to the occurrence of frailty associated with a known wasting disease such as heart failure, chronic obstructive pulmonary disease, tuberculosis, cancer, AIDS, etc. The dysregulation of several physiological systems, including the presence of malnutrition, chronic inflammation, and dysfunction of the immune system, nervous system, musculoskeletal and/or endocrine system, are the main characteristic of frailty.

Frailty and sarcopenia

With the development and application of the concept of frailty, some researchers put forward the term “frailty syndrome”. Frailty syndrome includes skeletal muscle loss, physical dysfunction, cognitive decline, heart and respiratory functional decline, body metabolic disorders and health-related symptoms [26]. Sarcopenia is the decrease of skeletal muscle mass, muscle power and muscle function [41]. Sarcopenia is one of the core pathological manifestations of frailty syndrome, which can exist alone or be accompanied by increased fat [42,43]. However, frailty has to be distinguished from sarcopenia. Whereas sarcopenia is reduced skeletal muscle mass or muscle strength, the core of frailty is reduced overall physical function. Frailty is associated with greater vulnerability to minor stresses and a decreased defense reaction. A small negative event can trigger a ‘domino effect’ and induce a series of steps leading to an overall functional decline. It is a condition in which multiple physiological functions are impaired and accumulated across multiple organ systems, and is not entirely related to the mass or function of the skeletal muscles. Currently, sarcopenia usually precedes frailty and is an important cause of frailty, so there are some common etiological and pathophysiological mechanisms between them.

Frailty and inflammation

Studies suggest that inflammation plays a key role in the pathophysiology of frailty, and that various inflammatory cytokines are significantly associated with the frailty index, including interleukin 6 (IL-6), C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and CXC chemokine ligand 10 (CXCL-10) [44,45]. Other studies have shown that the levels of IL-6 and CRP, and the white blood cell count and monocyte count, were significantly increased in patients with frailty [46,47]. IL-6 acts as a transcription factor and signal transduction factor, adversely affecting skeletal muscle, appetite, adaptive immune system function and cognitive function. Advanced glycation end products (AGEs) cause extensive cell damage through upregulation of inflammation, which is related to aging, chronic disease and death [48]. Coagulation markers including coagulation factor VIII fibrinogen, and D-dimer, have also been shown to be associated with frailty [49].

Frailty and the nervous system

Cognitive dysfunction and Alzheimer’s disease are both associated with aging, and numerous pathophysiological changes occur in both conditions, including impairment of the cerebral cortical and hippocampal neurons, structural and functional alterations of microglia, functional decreases of the central nervous system, and individuals become extremely sensitive to minor stress [50,51]. Studies have shown a temporal link between frailty, cognitive impairment and Alzheimer’s disease. Boyle and colleagues [52] found that physical frailty was associated with the incidence of mild cognitive impairment (HR = 1.63, 95% CI = 1.27-2.08) in a prospective cohort study of 750 older adults followed for 12 years. Higher levels of physical frailty were associated with a faster rate of decline in global cognition and five cognitive systems (episodic memory, semantic memory, working memory, perceptual speed, and visuospatial abilities). In a cohort study of 273 hospitalized
elderly patients over 75 years old, delirium was detected in 102 patients (mean Fi: 0.33). Among the patients with delirium, the median survival in fit patients was 359 days (95% CI = 118-600) compared with 88 days for those who were frail (95% CI = 5-171, P < 0.05) [53]. This study suggests that early recognition of frailty in delirium patients has an important impact on improving their clinical outcomes.

Frailty and the endocrine system

There is a growing consensus that the reactivity of the hypothalamic-pituitary-adrenal axis induced by inflammatory stimuli is greatly enhanced with aging [54]. The renin-angiotensin system and mitochondria are also altered by aging, which may affect the occurrence of sarcopenia and the inflammatory response, ultimately leading to frailty [55]. Insufficient secretion of corticosteroids, glucocorticoids, growth hormones, and androgens, as well as insulin resistance, have been proven to be closely related to frailty [56]. Cappola AR and colleagues performed a cross-sectional study of 494 elderly people aged 70-79 years, and found that multiple hormone deficiencies were more likely to lead to frailty than a single hormone deficiency, suggesting that frailty may be caused by broad endocrine system dysfunction rather than a specific type of hormone deficiency [57]. Pérez-Tasigchana RF et al. [58] found that metabolic syndrome, especially abdominal obesity, significantly increased the risk of frailty in a prospective cohort study of 1,499 participants over 60 years old who were followed for 3.5 years. Hyperglycemia is significantly correlated with the incidence of frailty [59].

Frailty and malnutrition

Nutritional disorders and malnutrition are important causes of frailty, and the nutritional status has a significant impact on frailty. Malnutrition is mainly related to energy deficiency and protein deficiency. It is characterized by increased catabolism, decreased anabolism, and poor immune function. It can lead to multi-system function decline, increased susceptibility to infection, and further aggravation of frailty. The decrease of myogen synthesis and sarcopenia caused by nutritional deficiency are important factors related to the occurrence and progression of frailty. A study using data from 802 persons aged 65 years or older participating in the InCHIANTI study showed that daily energy intake of ≤ 21 kcal/kg was significantly associated with frailty (OR = 1.24, 95% CI = 1.02-1.50), and a low intake of protein, vitamin D, vitamin E, vitamin C and folic acid was also significantly associated with frailty [60]. Chang SF et al. [61] found that frail individuals had a higher incidence of malnutrition in a community elderly population in Taiwan. Bollwein J et al. [62] showed that frailty was significantly correlated with the mini Nutritional Assessment (MNA) score, and malnutrition increases the risk of frailty [63]. Valentini A et al. [64] found that 38% of patients with a hip fracture had frailty, and 65% of them were at risk of malnutrition.

The BMI has a U-shaped relationship with frailty, which is similar to abdominal obesity [65]- the greater the waist circumference, the more severe the frailty. Abdominal obesity is a key factor associated with insulin resistance in elderly patients, and correlates with frailty through a variety of mechanisms, including inflammatory responses, oxidative stress, and the release of free fatty acids into the blood. However, obesity is related to diabetes, atherosclerotic disease, arthritis and other metabolic diseases, which may confound the association of obesity with frailty, but relevant research suggests that abdominal obesity is still associated with frailty and pre-frailty even when the above chronic complications are controlled.

Vitamin D plays an important role in protein synthesis, the regulation of calcium transport, and healthy bone development and physical function maintenance. It has been shown that 1,25-dihydroxyvitamin D can inhibit the secretion of IL-12 by antigen presenting cells, can enhance the anti-inflammatory effects of Th2 cells, and can weaken the pro-inflammatory effects of Th1 cells. Therefore, low 1,25-dihydroxyvitamin D levels may increase Th1 cytokine-mediated autogenetic diseases, including inflammatory bowel disease, rheumatoid arthritis, and Type 1 diabetes [66]. A study by van den Berg and colleagues found that vitamin D deficiency was closely associated with the course of frailty in a depressed older population [67]. An updated Cochrane review indicated that supplemental vitamin D and calcium may prevent hip or any type of fracture in post-menopausal women and older men [68], and this may underlie this impact on frailty. However, the use of vitamin D to reduce the risk of frailty or to treat the condition remains controversial, and large-scale trials and follow-up studies are required [69].

Interventions for Frailty

Exercise is currently believed to benefit the skeletal muscle-neuro-endocrine-immune system and may be the most effective intervention to improve physical function and the quality of life for frail people. Regular exercise can not only improve muscle strength, improve balance and prevent falls, but also plays a positive role in preventing dementia and depression, enhancing self-care ability, improving the quality of life and increasing overall happiness. Most exercise intervention research has combined exercise with flexibility, balance, resistance and endurance training. It has been reported that engaging in 30 minutes per day of aerobic or resistance exercise (such as sitting leg lifts, static squats against a wall, dumbbell lifts, elastic band pulls, etc.) twice a week can significantly improve the functional status and physical index in frail people [70]. Even the severely frail and super-elderly are likely to benefit from safely tolerated physical activity [71]. Recently, a multicenter, randomized, controlled trial was conducted by Kitzman DW and
colleagues to evaluate a transitional, tailored, progressive rehabilitation intervention to improve the physical function in older patients who were hospitalized for acute decompensated heart failure. A total of 349 patients were included [175 in the rehabilitation intervention group and 174 in the usual care (control) group]. At baseline, 97% of the subjects were frail or prefrail. Data showed that an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains (strength, balance, mobility, and endurance) resulted in greater improvement in physical function than usual care [72].

In terms of nutritional intervention, total nutrient supplementation, fortified protein supplementation, micronutrient supplementation (vitamin D, omega-3 polyunsaturated fatty acids and multivitamins), nutritional counseling and nutritional education are currently the main methods. Fiatarone MA et al. [71] studies 100 elderly frail patients (63 females, 37 males) with an average age of 87.1 ± 0.6 years old, and randomly divided them into 4 groups, including a resistance exercise group (resistance exercise, 3 times a week, 45 min each time), a resistance exercise and oral nutritional supplements (ONS) group (240 ml daily for 360 kcal), an ONS supplement group, and a placebo group, for a total of 10 weeks. The results showed that muscle strength increased significantly in the resistance exercise group with or without ONS, compared with the ONS group or placebo group. The total energy intake was significantly increased only in the exercising subjects who also received nutritional supplementation. The nutritional supplement alone had no effect on any primary outcome measure [71].

A randomized community trial showed that nutritional intervention can increase energy and nutrient intake, increase body weight and significantly improve the nutritional status in frail undernourished elderly people, but may not lead to any significant changes in muscle strength or body function [73].

Ng TP et al. [74] randomly divided 151 patients with frailty into 5 groups for 6 months of intervention, including a nutritional supplement group, cognitive training group, physical training group, combination therapy group and conventional care group. The frailty index, body mass index, knee extension strength, gait speed, and physical activity level were assessed every 3 months. The results showed that the frailty score and status over 12 months were reduced in all groups, including control subjects (15%), but were significantly higher (35.6% to 47.8%) in the nutritional (OR = 2.98), cognition (OR = 2.89), and physical (OR = 4.05) and combination (OR = 5.00) intervention groups. In recent years, multidisciplinary intervention programs to prevent falls in older frail people were proposed [75,76], which may also help frail older populations receive greater benefit from other interventions.

There is little research on pharmacological interventions for frailty. A randomized clinical trial showed that angiotensin converting enzyme (ACE) inhibitor treatment for 20 weeks in subjects aged 65 years and older who had problems with mobility or functional impairment significantly increased the mean 6-minute walking distance relative to the placebo group. There was also a significant impact on the health-related quality of life; while the mean score for part 1 of the EQ-5D questionnaire deteriorated over time in the placebo group, the quality of life was maintained in the perindopril group [77]. Testosterone replacement therapy can increase muscle mass and strength in hypogonadal and normal men, especially when combined with exercise [78]. However, testosterone can cause dyslipidemia and can have unpredictable effects on the prostate. Growth hormone-releasing hormone (GHRH) has also been shown to have positive effects on cognitive function in frail elderly patients. The use of drugs to prevent and treat frailty is an important area of future research [79].

Conclusions

Frailty is a common clinical syndrome in the elderly, with a high incidence in patients with cancer, cardiovascular system diseases, respiratory system diseases, malnutrition and other diseases or conditions. The occurrence of frailty indicates that the body’s ability to adapt to stress events is reduced, making it is easier for small insults to cause major issues with the body’s functionality and leading to a poorer clinical outcome. Early assessment and intervention with appropriate tools based on research objectives and clinical needs is of great significance for improving the health prognosis. Maintaining the internal homeostasis in balance may benefit an individual more than treating a specific underlying disease. Improving an individual’s nutritional status, recommending tolerable strengthening exercises, and developing individualized multi-factor intervention models are the best ways to prevent the adverse clinical outcomes of patients with frailty.

Conflict of Interest

The authors declare no conflict of interest associated with this manuscript.

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References

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33. Chong E, Ho E, Baldevarona-Llengo J, Chan M, Wu L, Tay L.


**Appendix [1]**

Criteria Used to Define Frailty

**Weight loss:** “In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?” If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year - current weight)/(weight in previous year) = K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year’s body weight), then frail for weight loss = Yes.

**Exhaustion:** Using the CES-D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked “How often in the last week did you feel this way?” 0 = rarely or none of the time (< 1 day), 1 = some or a little of the time (1-2 days), 2 = a moderate amount of the time (3-4 days), or 3 = most of the time. Subjects answering “2” or “3” to either of these questions are categorized as frail by the exhaustion criterion.

**Physical Activity:** Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. kcals per week expended...
are calculated using standardized algorithm. This variable is stratified by gender.

**Men:** Those with kcals of physical activity per week, 383 are frail.

**Women:** Those with kcals per week, 270 are frail.

**Walk Time:** stratified by gender and height (gender-specific cutoff a medium height).

<table>
<thead>
<tr>
<th>Men</th>
<th>Cutoff for Time to Walk 15 feet criterion for frailty</th>
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<tbody>
<tr>
<td>Height ≤ 173 cm</td>
<td>≥ 7 s</td>
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<tr>
<td>Height &gt; 173 cm</td>
<td>≥ 6 s</td>
</tr>
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</table>

**Women**

| Height ≤ 159 cm | ≥ 7 s |
| Height > 159 cm | ≥ 6 s |

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

<table>
<thead>
<tr>
<th>Men</th>
<th>Cutoff for grip strength criterion for frailty</th>
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<tbody>
<tr>
<td>BMI ≤ 24 kg/m²</td>
<td>≤ 29 kg</td>
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<tr>
<td>BMI 24.1-26 kg/m²</td>
<td>≤ 30 kg</td>
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<td>BMI 26.1-28 kg/m²</td>
<td>≤ 30 kg</td>
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<td>BMI &gt; 28 kg/m²</td>
<td>≤ 32 kg</td>
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<th>Women</th>
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<td>BMI ≤ 23 kg/m²</td>
<td>≤ 17 kg</td>
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<tr>
<td>BMI 23.1-26 kg/m²</td>
<td>≤ 17.3 kg</td>
</tr>
<tr>
<td>BMI 26.1-29 kg/m²</td>
<td>≤ 18 kg</td>
</tr>
<tr>
<td>BMI &gt; 29 kg/m²</td>
<td>≤ 21 kg</td>
</tr>
</tbody>
</table>