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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

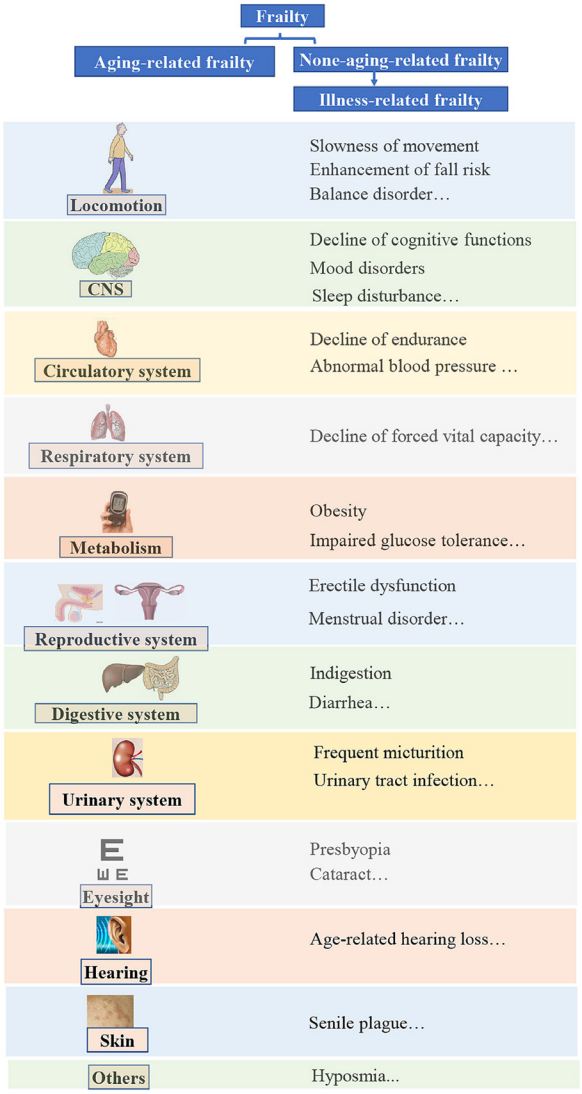

Figure 1. The potential physical changes associated with frailty.

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

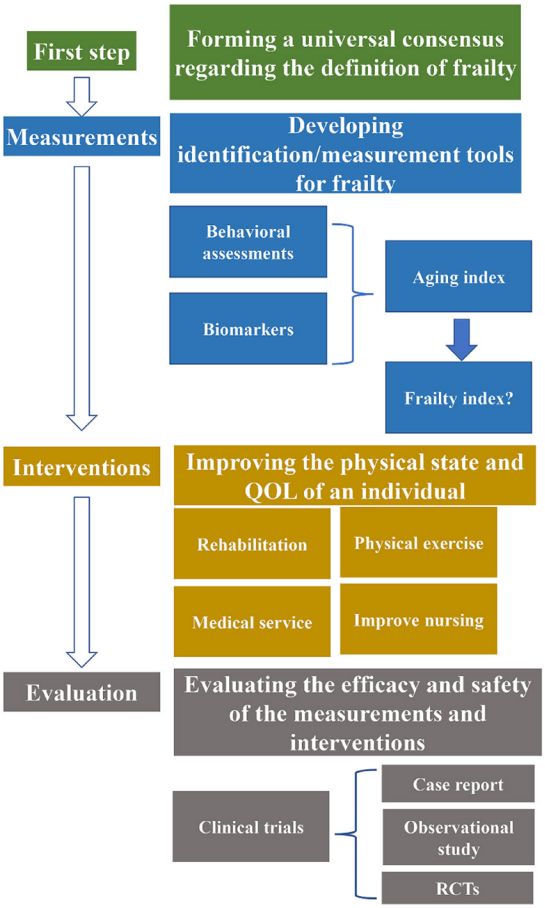

Figure 2. The future strategy to fight against frailty.

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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Policy Forum

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Healthy aging, early screening, and interventions for frailty in the elderly

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SUMMARY With the intensification of population aging worldwide, the health problems of the elderly have become a particular concern. Functional disability is a prominent problem in the aging of this population, resulting in the decreased quality of life of senile people. Risk factors for functional disability in the elderly include geriatric syndromes and the associated diseases such as frailty. The influence of frailty on the health of the elderly has been a hot topic in recent years. As a dynamic and reversible geriatric syndrome, it has become one of the important public health problems emerging around the world. Frailty lies between self-reliance and the need for care and is reversible. Reasonable preventive interventions can restore the elderly to an independent life. If no interventions are implemented, the elderly will face a dilemma. There is no gold standard for frailty screening around the world. In order to alleviate frailty in the elderly, many countries have conducted early screening for frailty, mainly focusing on nutrition, physical activity, and social participation, in order to detect and prevent frailty earlier and to reduce the incidence of frailty. This topic provides an overview of the current status of frailty, early screening for frailty, and the interventions for frailty in most countries of the world.

Keywords frailty, aging, strategy, early screening, management

1. Introduction

Population aging is accelerating around the world, and this demographic change will have important impacts on all aspects of society. In Asia, Japan has taken the lead in becoming the country with the highest aging rate in the world. The figures released by the Japanese Government in 2022 showed that the population over 65 years of age has reached 36.21 million, accounting for 28.9% of the total population (*i.e.*, the aging rate) (*1*). Similarly, China has become the country with the largest number of elderly people. The seventh national census released by China's National Bureau of Statistics (*2*) reported that by the end of 2020, China's population age 60 and over reached 264 million, accounting for 18.7% of the total population. Of these, 191 million were age 65 or older, accounting for 13.5%. In 2025, the proportion of senile people age 65 and above is expected to reach 14% of the total population and 30% of the total population in 2050 (Figure 1). According to the survey statistics, the average life expectancy of Chinese residents has increased from 77.3 years in 2019 to 78.2 years in 2021, and the healthy life expectancy of Chinese residents was 68.7 years in 2018, which means that these residents would live with disease for an average of 8-9 years (*3*). According to the latest data released by the World Health Organization (WHO), chronic diseases account for 6 of the top 10 causes of death around the world (*4*). Notably, most elderly people in China have chronic diseases such as diabetes and hypertension; the prevalence of chronic diseases in this population is 43.6% (*5*). Obviously, chronic diseases not only shorten the healthy life span of the elderly but also make the elderly more vulnerable to the risk of disease. Serious chronic diseases may even markedly affect the daily living and quality of life of the elderly. At the same time, a variety of diseases increase the number of elderly outpatients and hospitalizations, resulting in a sharp increase in medical costs and consumption of a large amount of medical resources. Therefore, population aging poses great challenges to health care worldwide (*6*).

The world's population is aging, and the current demographic and health shifts are contributing to a rapid increase in the number of people experiencing disability or declines in functioning for substantially larger periods of their lives (*7*). Disability is a prominent challenge

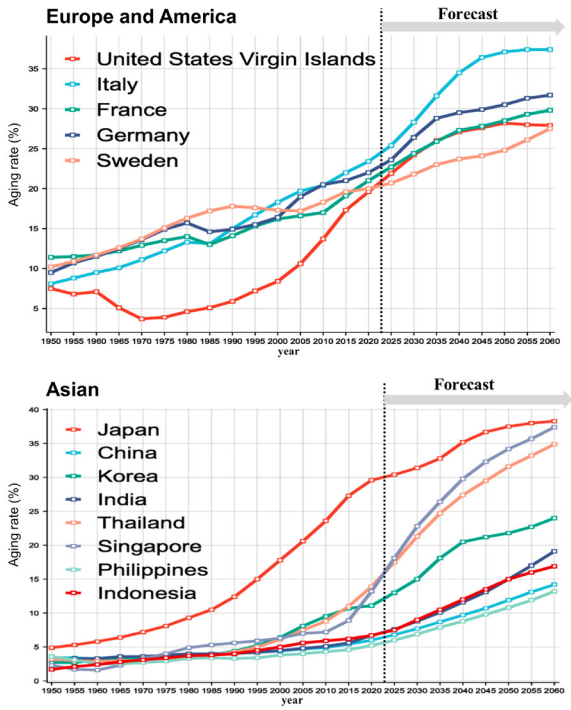

Figure 1. The aging rate of various countries in Europe, the US, and Asia (Source: United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition).

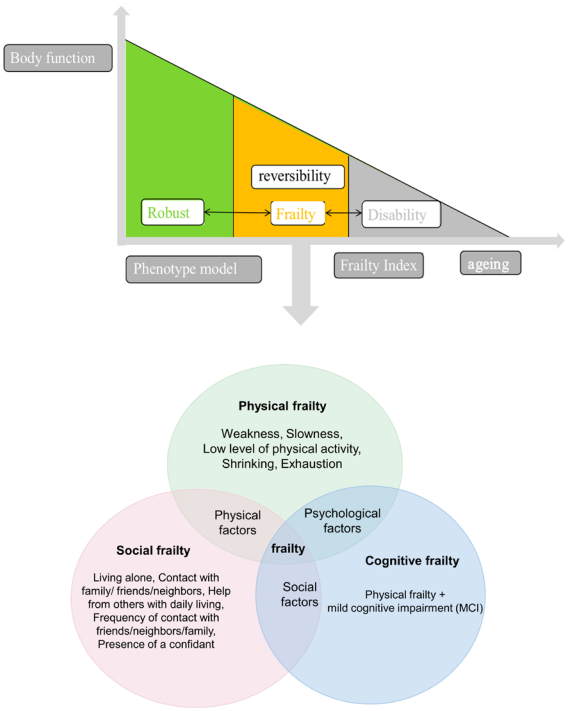

Figure 2. Diminished bodily functions and types. Frailty is a state between robust and disability. The probability of frailty increases with age and diminished physical functioning. Frailty can be determined by the Frailty Assessment Tools. Frailty consists of physical frailty, social frailty and cognitive frailty, which could individually or interact with each other to affect frailty by their respective counterpart factors.

in the process of population aging. One of the goals of the Healthy China action plan to promote the health of the elderly is to reduce the incidence of disability in the elderly. Moreover, the Core Message of Disability Prevention in Old Age (*8*) pointed out that risk factors for disability in the elderly include geriatric syndromes and diseases such as frailty. Frailty, a consequence of the interaction of the aging process and certain chronic diseases, compromises functional outcomes in the elderly and substantially increases their risk for developing disabilities and other adverse outcomes (*9*). Since frailty is a constantly evolving process, frailty in the elderly can be alleviated through certain interventions at an early stage. Consequently, actively promoting early screening and ascertaining effective interventions in frailty are of great significance to improving the quality of life of the elderly and reducing the public health burden.

2. The current status of frailty

Fried *et al*. provided the first standardized definition of the concept of frailty as a clinical syndrome with decreased internal stability and increased vulnerability due to the diminution of the functional reserves of multiple physiological systems (*10*). The course of frailty is a decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors. Being frail places a person at increased risk of adverse outcomes, including falls, hospitalization, and mortality (*11*). Although many researchers have paid attention to the problem of senile weakness since the 1970s and many different definitions have been proposed, there is still no uniform definition for clinical use (*12*) (Figure 2). According to the definition based on a Chinese "expert consensus", about 10% of the community-dwelling elderly age 60 and above, 15% of the elderly age 75-84, and about 25% of the elderly age 85 and above suffer from frailty (*13-15*). About 30% of the elderly are hospitalized (*16*). The incidence of frailty in the elderly in Japan is 7.4-8.7%, and the incidence of pre-frailty in the elderly is 40.8-48.1% (*17-18*). One can thus infer that the frail elderly and the pre-frail elderly account for 50% of the total number of elderly. As aging accelerates, so does the incidence of frailty. Subsequently, the physical and mental health problems caused by frailty become a problem that cannot be ignored. Frailty may have a serious impact on the quality of life, health status, and prognosis of individuals, including the decline of various physical functions and less ability to perform daily activities. Loss of appetite and changes in eating habits may also occur, leading to insufficient nutrient intake and accelerating the development of malnutrition and even resulting in a decline in personal self-confidence, anxiety, depression, and other psychological problems. These conditions ultimately require more frequent medical treatment and care and increase the consumption of medical resources and the economic

Table 1. Early screening characteristics in selected countries

Nation	Tools for early screening
China (*25,26*)	(1) clinical frailty scale (CFS), (2) frailty scale (FS), (3) Edmonton frailty scale (EFS), (4) Fried phenotype (FP), (5) Fried frailty phenotype (FFP), (6) frailty index (FI), (7) American frailty index (AFI), (8) Comprehensive Geriatric assessment (CGA), (9) Frailty Index-Comprehensive Geriatric assessment (FI-CGA), (10) Short Physical Performance Battery (SPPB), (11) Study of Osteoporotic Fractures (SOF).
US (*27-29*)	(1) frailty phenotype (FP), (2) Frail Scale (FS), (3) Study of Osteoporotic Fractures (SOF), (4) Short Physical Performance Battery (SPPB).
Canada (*30,31*)	(1) frailty index (FI), (2) clinical frailty scale (CFS), (3) Frailty Index-Comprehensive Geriatric assessment (FI-CGA), (4) Canadian Triage and Acuity Scale (CTAS), (5) Edmonton frailty scale (EFS), (6) The Canadian Study for Health and Aging Clinical Frailty Scale (CSHA-CSF).
Holland (*32-34*)	(1) Groningen Frailty Indicator (GFI), (2) Tilburg Frailty Indicator (TFI), (3) Comprehensive Frailty Assessment Instrument (CFAI).
Japan (*35-38*)	(1) Japan Frailty Scale (JFS), (2) Kihon Check-list (KCL), (3) frailty screening index (FSI), (4) frailty phenotype (FP).

burden. Early screening for frailty could protect the health and quality of life of the elderly, reduce the burden of medical care on the individual and his or her family, and promote the rational use of social resources to better meet the challenges of an aging society.

3. Screening for frailty

In recent years, the focus of medicine has shifted from the diagnosis and treatment of diseases to the early prevention of diseases in order to reduce and delay the development of diseases (*19*). The Task Force of the International Conference on Frailty and Sarcopenia Research (ICFSR) recommends that frailty be evaluated in all adults age 65 years and older by simple and effective assessment tools adapted to specific conditions. In addition, screening for possible vulnerability and evaluation of older adults in the early stages of frailty could help to reduce the likelihood of frailty (*20*). Comprehensive assessment of aging (CGA) is evaluated by physical function status, mental and psychological status, pain, sleep, and other items. Normally, it takes less than 5 minutes to complete all programs. These evaluations can be used in community health service centers and geriatric clinics to screen older adults with frailty-related risk factors. CGA allows for early detection of potential problems in the elderly and timely intervention, with the aim of promoting the health of the elderly and improving their quality of life (*21-23*). At present, there are around 67 frailty assessment tools available internationally and more are being developed (*24*). Table 1 shows that different countries have frailty assessment tools suited to their circumstances. The frailty phenotype and frailty screening index are also trusted assessment tools for frailty in all countries. A literature search of PubMed yielded frailty assessment tools, and these tools can be roughly divided into the following categories based on their use (Table 1): *i)* Assessment of frailty biomarkers (such as those detected in serum including inflammatory factors and hormones); *ii)* Different or specific frailty assessment tools; *iii)* Frailty risk factor assessment tools; *iv)* Screening criteria for inclusion or exclusion of subjects; *v)* Evaluation of the prevalence of frailty; *vi)* A clinical decision guide to evaluate the eligibility of elderly patients for surgery and the prognosis; *vii)* Prognostic indices to determine the effectiveness of interventions; and *viii)* Predictors or risk factors for a variety of age-related adverse health outcomes, including disability and death.

The frailty screening tools vary in their consistency, applicability, and effectiveness (*37,38*). For example, some frailty measures are more appropriate for community health settings, while others may be most effective for frailty screening or diagnosis in a hospital setting (*39*). In addition, different frailty screening tools are used for different patients with various diseases (*26*). However, a "gold standard" for frailty has not yet been established, resulting in the fact that screening and assessment tools for frailty are often combined. That means that the requirements for screening and assessment tools for frailty are different (*40*). The basic requirements for valid screening tools are simplicity, speed, and sensitivity. Assessment tools need to be highly accurate, practical, and supported by reasonable biological theories. In the future, our aim is to distinguish the most common frailty scales for screening and assessment, effectively helping researchers and medical personnel to select frailty tools more accurately in order to identify elderly people at high risk of frailty in an early stage. Our objective is to achieve early detection, early diagnosis, early treatment, and prompt intervention (*41*). Studies have shown that frailty screening for disease may improve overall outcomes (*42*). In future frailty screening, researchers should fully consider the purpose of assessment, resources, priorities, characteristics of screenees, and feasibility. They should select appropriate frailty assessment tools in order to take effective

measures to alleviate the existing health problems of the elderly in advance, prevent the progression of frailty, improve quality of life, and ultimately live a healthy life in old age.

4. Frailty interventions and management

4.1. Non-drug interventions and management

4.1.1. Exercise

Exercise is the first choice for the prevention and treatment of frailty. It can improve the physical functions, mental state, and activities of daily living (ADL) of the elderly, alleviate depressive symptoms, and reduce the risk of falling to effectively prevent frailty. There are many types of traditional exercises in China, including Tai chi, Five Animal Exercises, and sitting Baduanjin. Sitting Baduanjin can effectively prevent frailty in elderly patients, and especially psychological frailty and social frailty (*43,44*). Tai chi combined with resistance training also help to alleviate symptoms of frailty in the elderly (*45*). Among the exercises suitable for frail elderly, aerobic exercise is the foundation; strength training is the core; explosive strength training and flexibility training are auxiliary; and balance training and virtual training are complementary. A multi-component exercise intervention strategy using a variety of training methods is the best choice for prevention and treatment of asthenic syndrome in the elderly (*46*).

4.1.2. Nutrition

Nutrition plays a crucial role in the development and progression of frailty. The intake of a series of nutrients such as energy, protein, lipids, and vitamins decreases with age, resulting in undernutrition. Nutrition targets for healthy elderly people are as follows: *i)* Energy: The guiding value for energy intake in the general elderly population is recommended to be 20-30 kcal/kg. For elderly patients with malnutrition, low body weight, and stress, it can be increased to 30-40 kcal/kg (*47*); *ii)* Protein: According to data from the Health, Aging, and Body Composition study in the US, dietary total and animal protein intake were associated with an increase in lean mass in older people. Compared to American people, Japanese people consume a lower amount of dietary animal protein (8.9% for men and 8.8% women in Japan, and 10.2% for men and 10.1% for women in the US) (*48*). The better approach is to focus on quality protein, such as fish, milk, and eggs; *iii)* Carbohydrates: The recommended carbohydrate intake is 50-65% of total energy (*49*); *iv)* Fat: The standard daily fat intake per person is 8.22-12.50 g, and the standard daily animal fat intake per person is 25.40-36.80 g (*50*); *v)* Dietary fiber: The recommended intake is 17-19 g/d (*51*); *vi)*, Microelements and vitamins: Fruits and vegetables are rich in microelements such as vitamins, and the lower limit of vegetable intake for the elderly is 300-500 g/d, and the lower limit of fruit intake is 200-350 g/d (*52*).

4.1.3. Social environment

Seclusion and lack of communication with the outside world are phenomena of social frailty (*53*). Social frailty also affects physical frailty. In contrast to physical frailty, social frailty is associated with the subjective mindset of the elderly. A study has suggested that loneliness in general is not what affects frailty but actively engaging in activities. Therefore, preventing frailty by implementing interventions that promote older adults' active engagement may improve their quality of life (*54*).

In response to the COVID-19 pandemic, people are going out less often and have fewer opportunities to communicate with others. As information technology has continued to advance in recent years, VR technology mainly using a desktop computer, a large screen, and goggles is widely used in post-stroke cognitive rehabilitation training and balance and walking ability training for the elderly (*55,56*). As one benefit, it can solve the physical frailty caused by the inconvenience of going out. as another benefit, information technology can also alleviate social isolation caused by reduced human interaction in order to bring people closer together *via* remote means. Use of VR technology in the assessment and rehabilitation treatment of the elderly can both provide personalized and accurate care to improve the health status of the elderly and also offer health education support to the elderly to reduce their anxiety and mental depression.

4.2. Drug interventions and management

4.2.1. Polypharmacy and frailty

A hierarchical diagnosis and treatment policy is gradually being implemented in China. Since the establishment of the family doctor system in Shanghai in 2011, residents' trust and recognition of family doctors have gradually increased. Family doctors can promptly and comprehensively ascertain chronic diseases in the elderly and their medication status, which is conducive to avoiding redundant medication and over-dosage (*57*). Other important approaches are to enhance community medical centers, continuing to pay attention to the status of chronic diseases in the elderly in the community, tracking health status and medication, and making full use of the Internet and chronic disease management platforms. Moreover, timely health education, targeted treatment, and regular follow-up are also of great importance. The elderly should follow the doctor's advice so that medication is "reduced and more precise". A multidisciplinary geriatric medicine team can be

set up to participate in the multi-drug management of chronic comorbidities in the elderly it can further evaluate drug safety and efficacy in patients, promptly identify problems with drug treatment, and implement effective interventions (*58*). Senile patients should be advised to avoid self-treatment based on feelings and life experience and to reduce the abuse of non-prescription drugs, "folk remedies" and "secret recipes", and various health products. The elderly is encouraged to have regular health check-ups and seek medical attention whenever they notice new symptoms.

4.2.2. Chronic disease management and frailty

Around the world, the "big 5" chronic diseases are diabetes mellitus, cardiovascular disease, chronic respiratory disease, cancer, and stroke (*59*). The elderly often have chronic diseases such as diabetes and high blood pressure. A point worth noting is that chronic diseases are often poorly managed, resulting in debilitating phenomena. Improper management of diabetes in the elderly can easily lead to severe hypoglycemia. Severe hypoglycemia increases the risk of cognitive impairment, heart and muscle infarction, and stroke. To control hyperglycemia in the elderly, the Gerontological Society of America has made the following recommendations: *i)* The goal of blood sugar control varies according to the age, cognitive function, physical condition, and other attributes of different elderly people. *ii)* Selection of hypoglycemic drugs. Drugs with a low risk of hypoglycemia and few adverse reactions should be selected, following individualized selection. *iii)* Non-drug treatment. Hazuda *et al*. (*62*) noted that early lifestyle interventions had more advantages than taking metformin in preventing faltering in elderly patients with diabetes. Japanese researchers noted that nutritional management of elderly diabetic patients should transition from the prevention of metabolic syndrome to prevention of frailty (*63*). A varied diet and adequate energy intake are important to preventing frailty in diabetic patients (*64*). In addition, a study has shown that Baduanjin combined with cognitive training can slow the decline of cognitive function, alleviate frailty, and reduce the blood sugar level in elderly diabetic patients, and this exercise is suitable for clinical and community promotion (*65*).

The current relevant guidelines on elderly hypertension do not provide clear goals for reducing blood pressure in the frail population (*66*). The guidelines issued by the International Association of Hypertension (ISH) in 2020 recommended that for elderly people age 65 and above, if they can tolerate antihypertensive treatment, blood pressure should be reduced to 140/90 mmHg. However, personalized antihypertensive therapies need to be developed according to the specific conditions of patients; frailty, the ability to live independently and other aspects need to be assessed; and no clear target values for reducing blood pressure are suggested (*67*). Of particular concern is excessive lowering of blood pressure, which increases the risk of falls (*68*). The initiation of drug therapy and the target value for lowering blood pressure are individualized for patients with hypertension.

Chronic respiratory diseases (CRDs) had a high prevalence, a high rate of disability, a long course, and high treatment costs. Chronic Obstructive Pulmonary Disease (COPD) is particularly harmful. According to survey statistics, there are 212.3 million patients with COPD (200.4-225.1), and COPD was the primary cause of deaths from CRDs, accounting for 3.3 million (2.9–3.6) deaths (*69*). Multiple global initiatives have been developed over the past few decades to improve respiratory care, undoubtedly contributing to the global decline in the age-standardized burden of CRDs. The Practical Approach to Lung health (PAL) was another tool created by the WHO to improve the management of respiratory patients in primary healthcare settings, and especially in countries with weak health systems (*70*). In addition, other global initiatives focusing on COPD (GOLD) (*71*) have been developed to increase awareness and improve prevention, management, and access to effective treatments. A study in the UK has shown that frailty was associated with mortality from respiratory diseases, while healthy behavior was able to mediate frailty to a certain extent. Therefore, promotion of a healthy lifestyle may be able to substantially attenuate the contribution of frailty to mortality from respiratory diseases *(72*).

When a patient has a tumor, his or her body is invaded by the tumor, and the patient faces a series of stressors such as surgery, chemo radiotherapy, and psychology; in such cases, frailty is particularly common, with an incidence of 6-86% (*73*). The following recommendations are given for the management of cancer patients in China: no smoking, not drinking excessively, maintaining a normal weight, engaging in proper physical exercise, and eating more vegetables and fruits to significantly reduce the incidence of cancer. Maintaining a healthy lifestyle has significant public health benefits (*74*). The most effective measures for preventing and controlling malignant tumors are primary prevention targeting risk factors and etiology (*75)*. Early screening for disease plays a crucial role in detecting frailty. Prevention of frailty differs in different countries, and approaches focus on different psychological, physical, and social aspects (Table 2).

4.2.3. Frailty and novel coronavirus

In late October 2020, a paper in the Journal of the American Geriatrics Society compiled data from patients with COVID-19 and found that the determining factor of death was not age but the degree of frailty

Table 2. Interventions for and management of frailty around the world

Nation	Frailty prevention strategy
China (*78*)	1, Conduct systematic health education, 2. Raise the level of social support and strengthen health management for the elderly, 3. Regular comprehensive geriatric assessment, 4. A healthy lifestyle, 5. Personalized nutrition interventions, 6. Healthy exercise, 7. Cognitive training, 8. Fall prevention, 9. Mental health, 10. Management of comorbidities and polypharmacy.
Japan (*79*)	An integrated community-based care system, with nutrition (food and oral function), physical activity (activities of daily life, sports, *etc*.) and social engagement (social activity) as the three pillars of frailty prevention, paralleled by polypharmacy and chronic disease management.
South Korea (*80*)	In South Korea, where research on frailty prevention began in 2014, there have been fewer studies focusing on the mental and social aspects and more on the physical aspects. Research mainly concerns two aspects of frailty prevention, food and exercise. In the future, attention needs to be paid to the physical aspects as well as the mental and social aspects.
US (*81*)	Mainly concerning the three major aspects of frailty prevention (psychological, physical, and social), but also through the intake of nutritious food to reduce the possibility of frailty.
Canada (*82*)	Frail or pre-frail elderly people adopt nutritional strategies (protein-fortified foods and supplements, vitamin D) and comprehensive physical activity (aerobic exercise, resistance exercise, balance exercise, flexibility exercise, and muscle strengthening exercise), and rehabilitation training is recommended for frail elderly people to achieve the combination of physical activity and nutrition.
Singapore (*83*)	The elderly are encouraged to participate in society, and the infirm should be given group exercises, including aerobic, resistance, balance, and strength training. At the same time, increase nutritional intake.
Spain (*84*)	Effective interventions in Spain include exercise, nutrition, cognitive training, geriatric assessment management, and rehabilitation. Among them, exercise interventions varied in duration, frequency, and type of exercise, but all were effective in reducing the degree of weakness.
Holland (*85*)	The prevalence of frailty was reduced by enhancing physical exercise, nutritional supplementation, cognitive training, and combination therapy.
Germany (*86*)	More attention needs to be paid to ways to improve physical activity and muscle strength, as well as to the emergence of depressive symptoms, the prevention of falls, and the control of polypharmacy.

and disability (*85-87*). Weakness also reduces the protection from COVID-19 vaccines in humans (*88*). That same year, a study in the UK also confirmed that frailty was associated with a higher risk of death from severe pneumonia infections (*89-91*). The Journal of the European Geriatric Society also pointed out that the mortality rate of COVID-19 patients is closely related to frailty (*92-94*). The Brazilian Journal of Medicine reported that the increased frailty often associated with COVID-19 also increases the risk of death (*95,96*). Frailty has been recognized as a risk factor for severe and post-critical outcomes of COVID-19 (*97,98*).

5. Healthy aging

As aging occurs globally, the health of the elderly has become a hot issue. However, there are no universal or set indicators of frailty. A set of simple and feasible frailty indices would be conducive to identifying more frail patients. Taking Japan as an example, the life problems of the elderly are addressed through a comprehensive pension policy and pension system. The "integrated community-based care system" was developed as a national policy. The "integrated community-based care system" is a comprehensive guarantee of medical care, nursing, preventive care, housing, and livelihood maintenance. For example, enhanced medical collaboration, 24-hour home care, enhanced visiting nursing, and rehabilitation training are included. Care includes home visits, shopping, food delivery, and shower assistance. In the face of the increasing number of elderly people living alone or as couples, the construction and maintenance of barrier-free housing for the elderly and the disabled is also a guarantee for frail elderly.

In recent years, China has begun to implement a hierarchical diagnosis and treatment policy based on the medical experiences of other countries. The contracted family doctor service is the foundation for promoting the creation of a hierarchical diagnosis and treatment system, and it plays a positive role in promoting the continuous treatment of elderly patients. At present, this is only a pilot program in a few cities in China, but hopes are to establish a nationwide medical system to provide better living conditions for the elderly to help them enjoy their old age.

Various countries have taken active measures to prevent frailty mainly related to the three aspects of physical, psychological and social conditions as well as nutritional intake. As part of future global measures to prevent frailty, a set of systematic policies to prevent frailty should be formulated to deal with frailty globally,

to reduce the risk of frailty and the rate of admission and readmission in the elderly, and to improve their quality of life.

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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

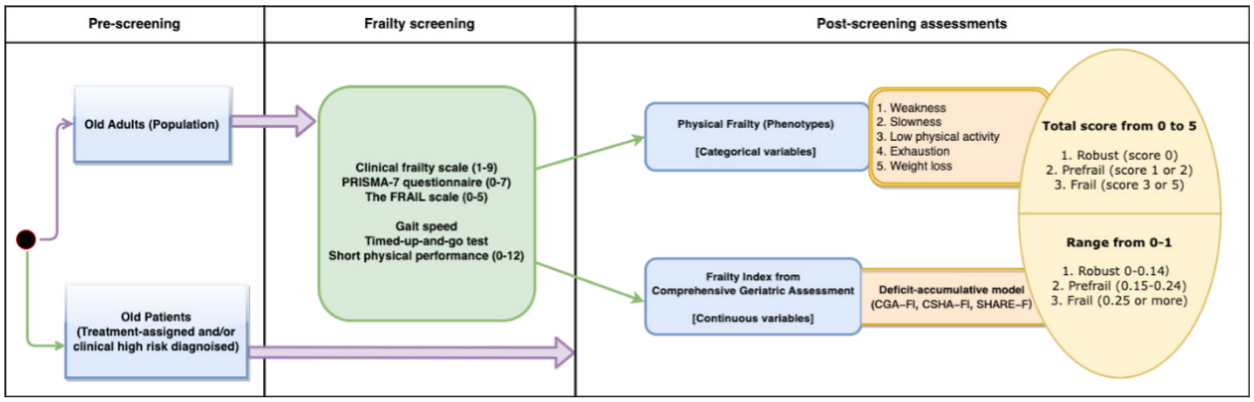

Figure 1. A flow diagram of the frailty assessment process.

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.

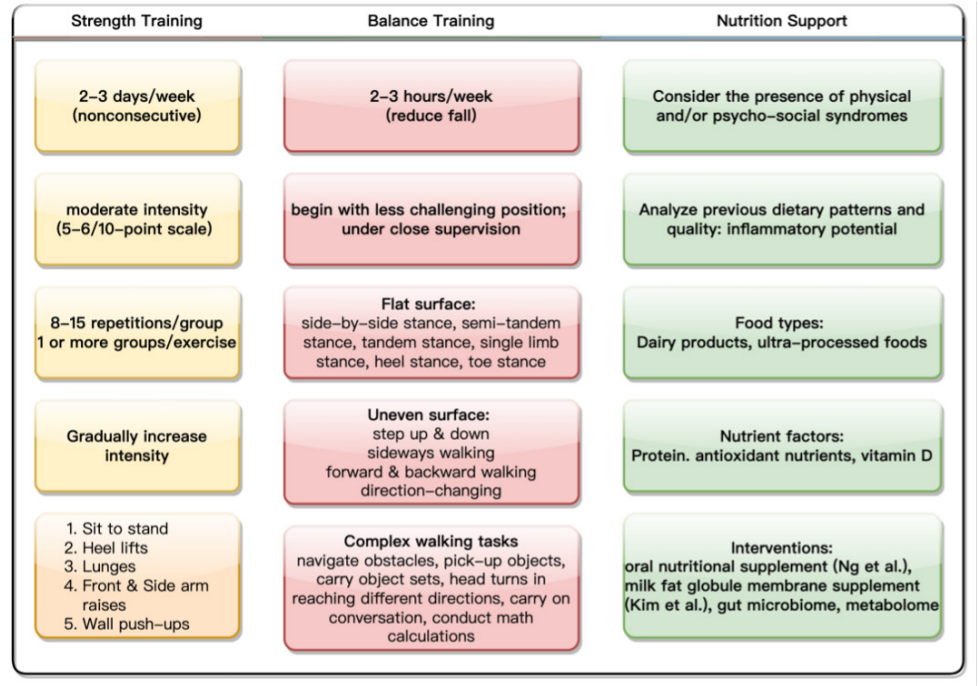

Figure 2. Elements of strength training, balance training, and nutrition support.

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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Review

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Neurosurgical perioperative management of frail elderly patients

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SUMMARY With the rapid increase in global aging, the prevalence of frailty is increasing and frailty has emerged as an emerging public health burden. Frail elderly patients suffer from reduced homeostatic reserve capacity, which is associated with a disproportionate decline in physical status after exposure to stress and an increased risk of adverse events. Frailty is closely associated with changes in the volume of the white and gray matter of the brain. Sarcopenia has been suggested to be an important component of frailty, and reductions in muscle strength and muscle mass lead to reductions in physical function and independence, which are critical factors contributing to poor prognosis. Approximately 10–32% of patients undergoing neurological surgery are frail, and the risk of frailty increases with age, which is significantly associated with the occurrence of adverse postoperative events (major complications, total duration of hospitalization, and need for discharge to a nursing facility). The postoperative mortality rate in severely frail patients is 9–11 times higher than that in non-frail individuals. Therefore, due attention must be paid to neurosurgical frailty and muscle assessment in elderly patients. Specialized interventions in the perioperative period of neurosurgery in frail elderly patients may improve their postoperative prognosis.

Keywords sarcopenia, aging, complication, prognosis

1. Introduction

Aging of the population is accelerating rapidly around the world. According to the World Population Prospects (2019 Revision), the number of people age 65 and over around the world exceeded the number of children under 5 for the first time in 2018 and is expected to increase from 9% of the total in 2019 to 16% in 2050; the number of people age 80 and over will increase from 143 million in 2019 to 426 million in 2050 (*1*). Japan, Finland, and Italy are currently the countries with the most serious aging problems (*2*). Aging has become one of the world's most serious medical and social issues. However, the most serious clinical symptom of an aging population is frailty.

In 1994, Rockwood *et al.* summarized frailty in the elderly as an "evolving concept" that has been developing for almost 20 years and is still evolving (*3*). The main characteristics of frailty are reduced function of multiple physiological systems, increased vulnerability to stress, and increased risk of falls, hospitalization, and death (*4*). The global burden of frailty is unknown, mainly because studies of frailty have focused on high-income countries and have used different definitions of frailty (*4*). A systematic evaluation of the prevalence of frailty in community-dwelling older people in several countries, involving a total of 61,500 participants, reported a widely varying prevalence ranging from 4.0% to 59.1%. The overall weighted prevalence of frailty was 10.7%, and the use of different frailty assessment criteria resulted in large differences in prevalence between studies (*5*). Evidence from the Canadian National Population Health Survey shows that the prevalence of frailty increases with age and that higher frailty indices require more health care services (*6*). The Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Expert Working Group recommends that all inpatients age 70 years and older be screened for frailty using a validated tool: the Clinical Frailty Scale (CFS), Hospital Frailty Risk Score (HFSC), a frailty scale, or a frailty index (*7*). The majority of frail older people have sarcopenia, which is considered an important component of frailty due to loss of muscle mass and strength, leading to imbalances and adverse outcomes (*8,9*). The ANZSSFR Expert Working Group recommends that sarcopenia/

muscle loss be assessed in all older (≥ 65 years) inpatients or younger patients with conditions that may increase the risk of sarcopenia, using established criteria (*7*). As the population ages, there has been a corresponding increase in the number of elderly patients undergoing neurosurgery (*10*). Frailty has been shown to be an independent risk factor for neurosurgical outcomes and is a better predictor of patient prognosis than traditional patient age (*11-14*). There is mounting evidence that frailty is strongly associated with a poor prognosis in patients after brain surgery. Frail patients having significantly higher rates of major complications, a longer total duration of hospitalization, a longer length of stay in the intensive care unit, and a higher risk of needing to be transferred to a nursing facility after discharge compared to non-frail patients; the postoperative mortality rate for severely frail patients is 9 to 11 times higher than that for non-frail patients (*11,14-17*). The current review focuses on the assessment and management of perioperative frailty and sarcopenia in elderly neurosurgical patients and it provides possible strategies to reduce the incidence of postoperative adverse events. The flow chart is shown in Figure 1.

2. The definition and etiology of frailty

Frailty is a complex group of age-related clinical conditions that typically involve a decline in the physiological functioning of multiple systems and organs, an increased susceptibility to stress, and a sudden and disproportionate change in health status following a seemingly mildly stressful event such as infection, trauma, or minor surgery. This initial stressful event is usually followed by a long recovery period and an inability to return to previous levels of functioning (*18,19*). The frailty phenotype has five criteria (weakness, slow gait, low physical activity, fatigue, and unintentional weight loss) and is further categorized sequentially as non-frailty (0 criteria), pre-frailty (1–2 criteria), and frailty (≥ 3 criteria) (*20*). Studies have shown that frailty affects approximately 10% of people age 65 years and older, increases with age, and is more common in females than in males (*5*). The development and progression of frailty are influenced by a variety of factors, including sociodemographic, biological, psychological, physical, and lifestyle factors. Sociodemographic factors include age, ethnic background, neighborhood, marital status, and level of education. Psychological factors mainly

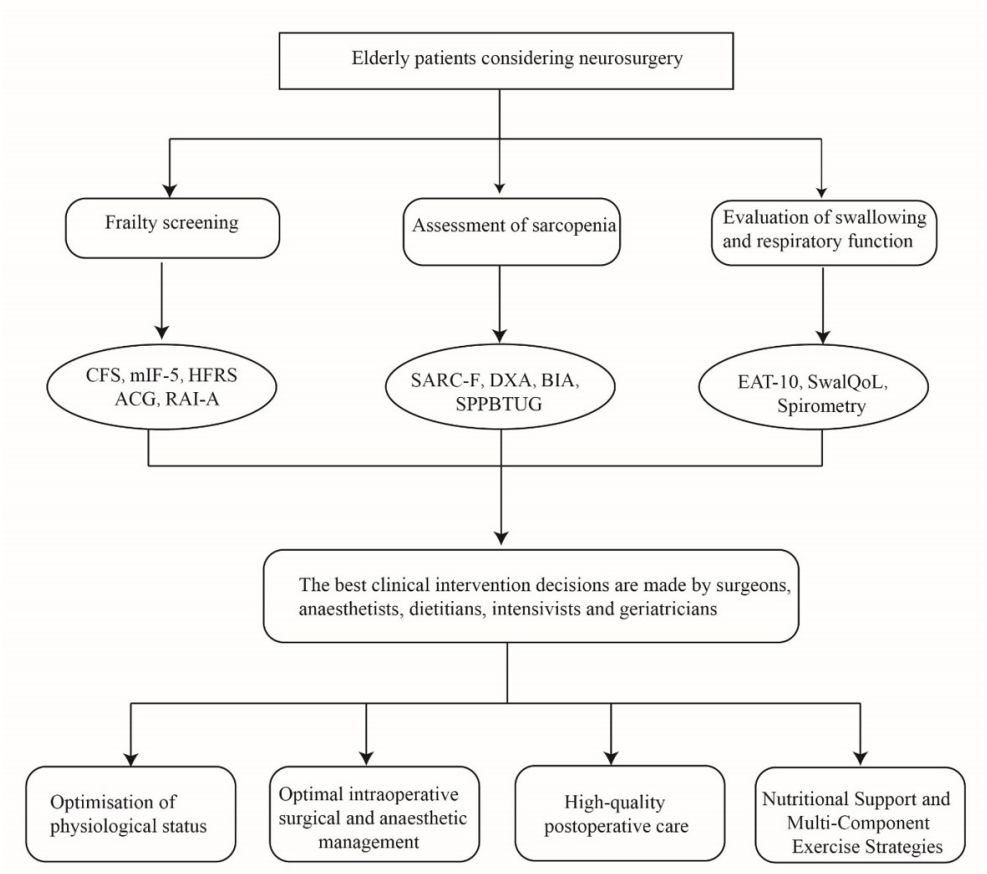

Figure 1. Flowchart of recommendations for elderly patients for the perioperative period of neurosurgery. Abbreviations: ACG, adjusted clinical groups; BIA, bioelectrical impedance analysis; CFS, clinical frailty scale; DXA, dual-energy X-ray absorptiometry; EAT-10, Eating Assessment Tool-10; HFRS, Hospital Frailty Risk Score; mIF-5, Five-factor Modified Frailty Index; RAI-A, Risk Analysis Index-Administrative; SARC-F, Simple Five-item Questionnaire; SPPB, Short Physical Performance Battery; SwalQoL, Swallowing Quality of Life; TUG, timed-up-and-go test.

include depressive states. Lifestyle factors include diet quality and fruit and vegetable intake. Physical factors include chronic diseases (mainly diabetes, obesity, and cardiovascular diseases) and physical inactivity or a sedentary lifestyle (*4,21-23*). In addition, multimorbidity is a risk factor for frailty, leading to imbalances in multiple physiological regulatory systems (*24,25*). According to Heart, stroke and vascular disease-Australian facts, 1.2 million Australians age 18 years and over had one or more conditions related to heart, stroke, or vascular disease in 2017–2018 (*26*). A meta-analysis of multimorbidity and frailty involving a total of 78,122 participants found that the prevalence of multimorbidity among frail people was 72% and the prevalence of frailty among those with multimorbidity was 16% (*27*). The same meta-analysis noted a bidirectional association between multimorbidity and frailty. Emerging evidence suggests that changes in cognitive reserve, or brain reserve, contribute to the development and progression of frailty during the aging process. For example, established features of brain aging – grey matter volume and total white matter hyperintensities – are associated with a wide range of physical and mental health measures (*28-30*). Severity of frailty was correlated with increased total white matter hyperintensities and reduced grey matter volume, particularly in subcortical brain regions, that partially mediated the association between frailty and cognitive decline, poor mental health, and an unhealthy lifestyle (*30*). Resting-state functional MRI data from the Irish Longitudinal Study on Aging (TILDA) showed that Aβ deposition in specific brain regions is associated with worsening frailty in older adults (*31*). Frailty is a category of age-related clinical syndromes influenced by lifestyle, psychological, and physical factors. It is also closely related to changes in brain reserve and structure during aging.

3. The intrinsic link between aging and frailty

Aging is a natural evolutionary process influenced by genetic, environmental, and epigenetic factors. The organism experiences inflammation and endothelial and vascular dysfunction following everyday injuries and infections. The organism repairs the damage at a cellular and tissue level and in the process of repair causes an accumulation of scarring, leading to gradual tissue degeneration and a decline in the physiological reserve function of organs such as the brain, endocrine system, immune system, and skeletal muscles, resulting in frailty and aging (*32-35*). Physiological decline may accelerate as frailty worsens (*36*), leading to deterioration in the functioning of multiple physiological systems that may contribute to a further decline in reserve function. Frail physical status changes disproportionately after exposure to stressful events, leading to an increased risk of adverse outcomes such as falls, delirium, and disability (*35*). In a study of the association between frailty and multi-system physiological disorders in older women, assessment of eight physiological system markers (*e.g.,* anemia, inflammation, and insulin-like growth factor-1) in 1,002 women age 70–79 years found that multi-system physiological abnormalities were a better predictor of frailty than single-system abnormalities. Abnormalities in multiple physiological systems may disrupt the body's homeostasis and adaptive capacity, leading to greater frailty and increased risk of adverse outcomes (*37*). Based on an analysis of data on 37 biomarkers in six physiological systems (lipids, immunity, oxygen transport, liver function, vitamins, and electrolytes) from 33,000 individuals, Li *et al.* found that dysregulation of the homeostasis of multiple systems occurs simultaneously in aging, that no one system is significantly better than another, and that dysregulation of multi-system homeostasis significantly predicts multiple health outcomes, including frailty (*38*). With aging, multiple systems become dysfunctional, function gradually declines, physiological reserves decrease, and the likelihood of frailty increases. However, there is a certain degree of heterogeneity in body function among individuals of the same age (*39*), so one cannot rely solely on age to evaluate the organ reserve capacity of patients. Frailty can better reflect the organ function of patients than age.

4. Sarcopenia and frailty

The concept of sarcopenia was first mentioned in 1988 by Irving Rosenberg, who noted that "no single feature of age-related decline is more striking than the decline in lean body mass, which affects ambulation, mobility, energy intake, overall nutrient intake and status, independence, and breathing" (*40*). In 2016, the World Health Organization (WHO) recognized sarcopenia as a separate disease, code M62.84 in the ICD-10-CM (*41*). The European Working Group on Sarcopenia in the Elderly (EWGSOP) defines sarcopenia as a syndrome characterized by progressive and systemic loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life (QoL), and death (*8*). The diagnostic criteria for sarcopenia are low muscle mass and strength or low physical performance (*8*). Sarcopenia is present in the majority of frail older people and is due to a progressive and systemic loss of skeletal muscle strength and mass with age (*8,9*). Many factors contribute to sarcopenia, including the body's normal aging process, the effects of early physical development, a bedridden or sedentary lifestyle, poor diet, chronic diseases, and medications (*8*). The five criteria for the frailty phenotype are strongly associated with sarcopenia, which has been described as the biological substrate of frailty (*42-44*). There is a growing body of evidence for endocrine dysfunction in frail patients. Deficiencies of certain hormones in the body are associated with loss of muscle mass (*8*).

A study on the health and aging of women, in which serum levels of total insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone sulfate, and free testosterone were examined in relation to frailty status (non-frail, prefrail, or frail) in 494 women age 70–79 years, found that individuals with anabolic hormonal deficiency were more likely to be frail, suggesting that frailty syndromes may involve systemic endocrine disruption (*45*). In a study of 214 older adults age 80–90 years, higher cortisol levels and delayed circadian variation were observed in frail older women (*46*). Cortisol promotes myogenic fiber degradation and inhibits protein synthesis to stimulate muscle atrophy (*18*), further contributing to sarcopenia syndrome. Insulin-like growth factors (IGFs) are a class of small peptides that increase the anabolic activity of many cells, with particularly important roles in neuronal plasticity and skeletal muscle strength (*47*). IGFs increase muscle strength by stimulating an increase in myoblast production, activating muscle cell hypertrophy, and inhibiting muscle proteolysis (*18*,*48*), while secretion of IGFs decreases in frail patients (*45*). By directly stimulating androgen receptors in skeletal muscle and activating the IGF-1 signaling pathway, testosterone increases muscle contractile protein synthesis (*49*). Research has shown that testosterone levels decline with age, and data suggest that bioavailable testosterone declines at a rate of approximately 2% per year in middle-aged men (*50*). Several epidemiological studies that have reported that low testosterone is associated with frailty (*51,52*). In addition, the production of vitamin D, the thyroid hormone, has also been shown to be involved in frailty and sarcopenia (*53,54*). Frailty and sarcopenia are closely related. On the one hand, sarcopenia is the biological basis of frailty, and on the other hand, the effects on endocrine hormones during the development and progression of frailty can further exacerbate sarcopenia.

5. Post-neurosurgical complications in frail patients

Frailty is strongly associated with the occurrence of adverse clinical outcomes after surgery, and frail patients have an increased risk of complications and mortality after surgery (*55*). Frailty is associated with increased mortality in patients after surgery. A cohort study of 432,828 patients suggested that low- and moderate-stress procedures may be risky in both frail and very frail patients, who had high rates of postoperative mortality (*55*). In neurosurgery, there is growing evidence that the presence of preoperative symptoms of frailty is significantly associated with a higher incidence of adverse events after neurosurgery (*12,56*). Based on data from the National Inpatient Sample (NIS), a retrospective study found that patients diagnosed with subarachnoid hemorrhage or cerebral hemorrhage who underwent surgery for aneurysm repair between 2005 and 2014 had an overall prevalence of preoperative frailty of 11.2% and that frail patients had an increased risk of postoperative tracheotomy, gastrostomy tube placement, and associated complications (*12*). Multivariate analysis showed that frailty was strongly associated with an increased risk of postoperative complications (aOR: 3.29, 95% CI: 2.55–4.25) and an increased risk of discharge to institutional care (aOR 2.50, 95% CI: 2.10–2.97) (*12*). Using the National Surgical Quality Improvement Program (NSQIP) database (2015–2019), Cole *et al.* found that 14.6% of patients who underwent resection of intracranial meningiomas (n = 5,818) were frail according to a five-factor modified frailty index (mFI-5) ≥ 2. Of these, 12.8% were generally frail and 1.8% were severely frail ((mFI-5) ≥ 3). In addition, severely frail patients had an increased risk of death (OR: 11.17, 95% CI: 3.45–36.19), a higher rate of complications (OR: 4.37, 95% CI: 2.68–7.12), and a longer duration of hospitalization (OR: 4.28, 95% CI: 2.74–6.68) compared to non-frail patients (*13*). The same study showed that the odds ratio (OR) and effect sizes of increasing frailty grade are better predictors of prognosis than age. Tang *et al.* retrospectively analyzed data on patients who underwent microsurgery for cerebral arteriovenous malformations (AVM) nationwide from 2002–2017, and they identified a new predictor of frailty, the AVM-5. They then compared the AVM-5 to the 5-factor modified frailty index (mFI), the 11-factor modified frailty index (mFI-11), and the Charlson comorbidity index (CCI). Frail admissions were predicted at a rate of 32% by the AVM-5, 8.3% by the mFI-5, 14.3% by the mFI-11, and 20.8% by the CCI. In addition, the frailty predictor AVM-5 was superior to other indicators in predicting major complications, postoperative mortality, and the total duration of hospitalization in microsurgery for cerebral arteriovenous malformations (*14*). Therefore, the mFI-5, mFI-11, and CCI can be used as complements to assess frailty in patients undergoing microsurgery for arteriovenous malformations, although the AVM-5 has some advantages over age and the mFI-5, mFI-11, and CCI. Frail patients with traumatic brain injury (TBI) had higher morbidity and mortality rates from complications compared to non-frail patients with traumatic intracranial hemorrhage according to an analysis of data from 691,821 TBI patients enrolled in the National Trauma Database (NTD) between 2007 and 2017 (*56*). A large multi-center data review evaluating the independent impact of frailty on brain tumor resection (BTR) showed that higher scores on the Risk Analysis Index-Administrative (RAI-A) were associated with an increased risk of adverse outcomes, including in-hospital mortality, non-routine discharge, and major complications (*11*). The RAI-A is considered to be a useful tool for the preoperative risk assessment of brain tumor patients and can be used as a basis for the risk-benefit assessment of brain tumor resection. Current studies have demonstrated that frail patients undergoing various types of neurosurgery have a significantly

Table 1. The effect of frailty on patients after neurosurgery

Reference	Disease	Mean age (years)	Method	Criteria	Frailty (%)	Postoperative adverse outcomes (frail *vs.* non-frail group)			
						Frailty Score	Outcome	OR	95% CI
Tang *et al.* (*56*)	TBI	57.6	mFI-5	mFI-5 ≥ 2	18	mFI-5 ≥ 2	in-hospital mortality	1.36	1.32–1.39
							major complication	1.06	1.04–1.07
							ICU LOS	1.11	1.10–1.12
							total LOS	1.13	1.11–1.14
Guo *et al.* (*12*)	aSAH	54.8	ACG	ACG ≥1	11.2	ACG ≥1	major complication	3.29	2.55–4.25
							discharged to institutional care	2.5	2.10–2.97
							in-hospital mortality	0.4	0.33–0.49
Thommen *et al.* (*11*)	BT	59	RAI-A	RAI-A >25	28.7	RAI-A 41–45	in-hospital mortality	4.3	2.1–8.9
							major complication	2.2	1.6–3.0
						RAI-A >45	in-hospital mortality	9.5	3.9–22.9
							major complication	2.5	1.5–4.1
Huq *et al.* (*60*)	BT	55.5	mFI-5	mFI-5 ≥ 2	19	mFI-5 ≥ 2	total LOS	1.38	0.96–1.80
							respiratory failure	1.55	1.01–2.40
							physiological/metabolic derangement	3.66	2.13–6.28
Cole *et al.* (*13*)	Meningioma	59	mFI-5	mFI-5 ≥ 2	14.6	mFI-5 ≥3	in-hospital mortality	11.17	3.45–36.19
							major complication	4.15	2.46–6.99
							eLOS	4.28	2.74–6.68
Jimenez *et al.* (*16*)	BT	55.3	HFRS	HFRS >15	8.2	HFRS >15	Non-routine discharge	1.14	1.12–1.17
							major complication	1.14	1.11–1.17
							90-day mortality	1.03	0.99–1.08

Abbreviations: ACG, adjusted clinical groups; aSAH, aneurysmal subarachnoid hemorrhage; BTR, brain tumor resection; eLOS, extended length of stay in hospital; HFRS, Hospital Frailty Risk Score; ICU, intensive care unit; mFI-5, Five-factor Modified Frailty Index; OR, odds ratio; RAI-A, Risk Analysis Index-Administrative; TBI, traumatic brain injury.

increased risk of a poor postoperative prognosis, as shown in Table 1. Frailty is a dynamic process. In frail patients undergoing neurosurgery, symptoms of frailty may be exacerbated, leading to an increased risk of complications and death. Conducting a preoperative assessment of frailty in neurosurgical patients and improving the perioperative management of frail patients will help to reduce the incidence of adverse events and improve prognosis for patients.

6. Management of postoperative frailty in neurosurgery

6.1. Frailty combined with biological age

With the aging of the world's population, a number of clinical studies have been conducted to investigate the relationship between actual age and various clinical outcomes, including surgery. A correlation between biological age and poor clinical prognosis is corroborated by a large amount of data. However, physiologic age is an immutable risk factor with obvious limitations as a study variable, so it should not be used as the sole determinant in making surgical decisions (*13,56,57*). In recent years, evidence has increasingly revealed that poor prognosis is related not only to the patient's age but also to the patient's level of frailty. The days of age being the sole determinant of outcome are over, and a patient's level of frailty should be part of the clinical decision-making process (*57,58*). Although there is no uniform assessment strategy for frailty, the finding that frail patients are more likely to experience adverse events postoperatively is consistent among studies (*14,59-61*). In a correlative study of 980 elderly oncology patients (age ≥ 75 years) who underwent a preoperative comprehensive geriatric assessment (CGA), frailty (stratified by the number of impairments in the geriatric assessment) was associated with 6-month mortality after surgery (OR: 1.14 for each unit increase in the CGA score; $p = 0.01$) (*62*). Another study of the impact of frailty on clinical outcomes after aneurysmal subarachnoid hemorrhage found that frailty was significantly associated with an increased risk of postoperative tracheostomy or gastrostomy tube placement and of postoperative complications. A risk-stratified analysis of patients undergoing surgery found that postoperative effects were more pronounced in frail patients under the age of 65 years (*12*). Another study on the association between frailty status and age and outcomes in patients undergoing surgery for intracranial meningiomas showed that increasing frailty was a better predictor of adverse postoperative outcomes than age, based on the OR and effect size (*13*). An assessment of frailty should be performed in elderly patients being considered for neurosurgery, rather than simply considering the actual age of the patient.

6.2. Outpatient screening of elderly patients for frailty and sarcopenia

Frailty and sarcopenia screening tools can help surgeons assess their patients' frailty and muscle status in a timely manner in an outpatient setting. Currently, the

CFS (*63*), Hospital Frailty Risk Score (HFRS) (*64*), CGA (*65*), frailty indices such as the 11-factor and 5-factor modified frailty indices (mFI-11 and mFI-5) (*66*), and the Risk Analysis Index (RAI) (*11*) are commonly used as screening indices to assess frailty in neurosurgery. Because of its simplicity and ease of use, the CFS is generally used in community settings. However, the HFRS is the most widely used screening index in the acute phase of the disease. The CGA-derived frailty index is commonly used to screen frail patients in population screening. The RAI has been shown to be a useful predictor of postoperative prognosis in neurosurgical patients and has been shown to be a particularly effective predictor of mortality. Jimenez *et al.* used the HFRS to predict postoperative outcomes in 2,518 patients with intracranial tumors and found that the HFRS was significantly and independently associated with postoperative complications (OR: 1.14, $p < 0.0001$), duration of hospitalization (coefficient = 0.50, $p < 0.0001$), increased hospital expenses (coefficient = 1,917.49, $p < 0.0001$), nonroutine discharge (OR: 1.14, $p < 0.0001$), and 90-day readmission (OR: 1.06, $p < 0.0001$) (*16*). Therefore, the HFRS is considered to be a valid predictor of postoperative outcomes in patients with intracranial tumors. Different frailty screening indicators have different effects on the assessment of frailty. Recent clinical studies have confirmed that the American Society of Anesthesiologists (ASA) score and the modified CCI have better predictive ability in preoperative risk stratification for spinal tumor surgery. In addition, the HFRS effectively predicts major postoperative complications and total duration of hospitalization in patients with intracranial tumors. However, the CFS is highly applicable in predicting overall survival in patients after resection of high-grade gliomas. The mFI-5 has been shown to be a valid indicator of frailty in patients with TBI and internal hemorrhage. The AVM-5 is significantly superior to other screening criteria in the microsurgical evaluation of arteriovenous malformations. The RAI-A has a higher predictive power for postoperative mortality in frail patients compared to other assessment measures (*11,14-16,56,67*).

Sarcopenia and frailty are related and there is a partial overlap between the two. This is especially true in terms of the parameter of impaired physical functioning, which is present in close to half of frail patients (*41,68*). Muscle tissue loss is inevitable in neurosurgical patients on postoperative bed rest, and it is most rapid initially due to inactivity (*69-71*). Trappe *et al.* reported a 29% reduction in the volume of the quadriceps muscle in young women after 21 days of bed rest (*72*). Preoperative evaluation of sarcopenia (loss of muscle mass and strength) is necessary in neurosurgical patients. This is in line with the recommendations of the ANZSSFR Expert Working Group to assess sarcopenia in inpatients age 65 years and older in a hospital setting. The EWGSOP2 recommends a pathway of "detection-assessment-confirmation-condition" (*73*) for assessing the presence of sarcopenia in clinical settings, where patients with sarcopenia are first identified with the SARC-F questionnaire, then assessed with the chair stand test, muscle quantity or quality is subsequently confirmed with dual energy X-ray absorptiometry (DXA) or bioelectric impedance analysis (BIA), and patients are finally further assessed for physical function status (*41,73*). Assessment of sarcopenia and related scales are shown in Table 2 (*73*). Patients with cranial tumors also need to be assessed for respiratory and swallowing function. Respiratory complications such as aspiration pneumonia and pulmonary infection are most common in debilitated

Table 2. Tools for the diagnosis and general assessment of sarcopenia

Criteria	Evaluation instruments	Cut-off points for sarcopenia	
		Cut-off points for men	Cut-off points for women
i) Low muscle strength	SARC-F questionnaire screening, Chair stand test, Grip strength	Chair stand > 15 s for five rises, Grip strength < 27 kg	Grip strength < 16 kg
ii) Low muscle quantity or quality	Appendicular skeletal muscle mass (ASMM) measured with dual energy X-ray absorptiometry (DXA), Total body skeletal muscle mass (SMM) or ASMM predicted with bioelectric impedance analysis (BIA), Cross-sectional area of the lumbar spine muscle according to CT or MRI	ASMM < 20 kg, ASMM/ height^2 < 7.0 kg/m^2	ASMM < 15 kg, ASMM/ height^2 < 5.5 kg/m^2
iii) Low physical performance	Gait speed (NIH Toolbox 4-meter Walk Gait Speed Test), Short Physical Performance Battery (SPPB), Timed-up-and-go test (TUG), 400-meter walk or long-distance corridor walk (400-m walk)	Gait speed ≤ 0.8 m/s, 400-m walk non-completion, 400-m walk ≥ 6 min for completion	SPPB ≤ 8 points, TUG ≥ 20 s, 400-m walk non-completion, 400-m walk ≥ 6 min for completion

Criterion *i*) identifies probable sarcopenia. Additional documentation of criterion *ii*) confirms the diagnosis. Sarcopenia is considered severe when criteria *i*), *ii*), and *iii*) are all met.

postoperative patients; dysphagia is a major cause of serious postoperative complications. Preoperative respiratory and swallowing dysfunction are significantly associated with early postoperative complications and mortality in neurosurgical patients (*74,75*). Respiratory function can be assessed by pulmonary function and swallowing function is screened for with the Eating Assessment Tool-10 (EAT-10) or the Swallowing Quality of Life (SwalQoL) questionnaire (*76-78*). Screening and assessment of frailty, sarcopenia, swallowing, and respiratory function prior to neurosurgery in elderly patients can help medical staff, patients, and their caregivers to formulate a rational and individualized treatment plan.

6.3. Perioperative management of frail patients

Frail patients who have undergone neurosurgery have a higher risk of short- and long-term complications as well as a higher mortality rate. Common complications in these patients include somatic complications and functional and cognitive decline (*78*). Surgical management facilitates the improvement of patients' surgical success and reduces the incidence of complications and mortality. The management process mainly includes frailty screening, optimization of physiological status, preoperative assessment, intraoperative management, and postoperative management in a community nursing program (CNP) as shown in Figure 2. New guidelines for the perioperative care of frail patients undergoing elective and emergency surgery from the Centre for Perioperative Care and the British Geriatrics Society (2021) recommend that all patients with a CFS ≥ 5 should undergo CGA and optimization prior to surgery (*79*). Optimization of physiologic status generally includes smoking cessation, inspiratory muscle training,

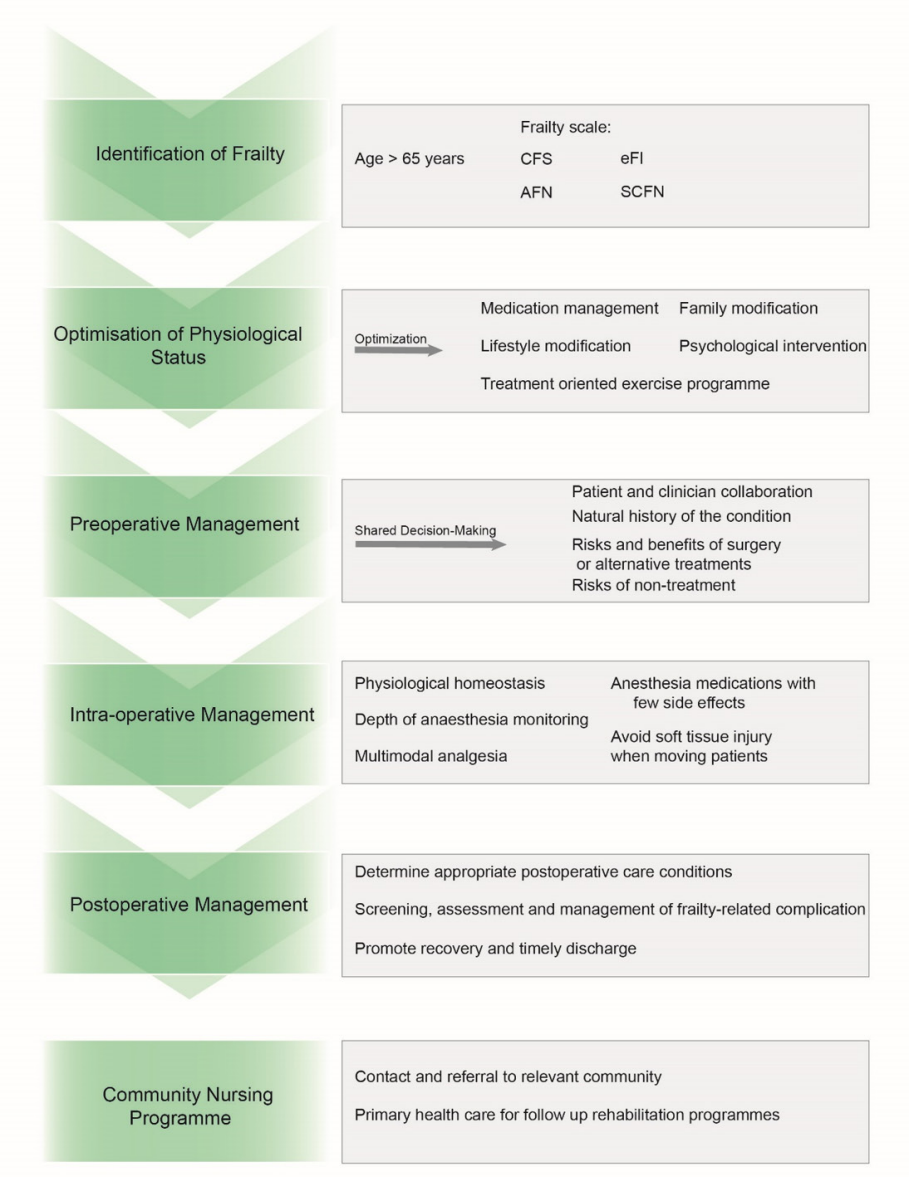

Figure 2. Guidelines for perioperative treatment of frail patients. Abbreviations: AFN, acute frailty network; eFI, electronic frailty index; CFS, clinical frailty scale; CNP, community nursing program; SDM, shared decision-making; SCFN, specialized clinical frailty network.

exercise, and physical therapy. Studies have shown that smoking cessation and inspiratory muscle training in patients with shortness of breath can reduce the duration of hospitalization after routine surgery. In addition, nutritional rehabilitation under the guidance of a dietician is beneficial to optimize the physiological state of patients with malnutrition and loss of appetite. Cognitive-behavioral therapy may be appropriate for patients with excessive anxiety or diminished cognitive function. Moreover, reducing sedentary behavior, regular sitting and standing exercises, and short walks can help improve exercise tolerance (*79-81*). The decision to proceed with surgery in a frail patient requires the involvement of the patient, family, and clinician in the decision-making process, including discussion of the natural progression of the disease, the advantages and disadvantages of surgery or alternative therapies, and the consequences of not undergoing treatment (*82*). In order to make the best medical decision for each individual at any given time, the best medical evidence available needs to be consulted (*83*). During surgery and anesthesia, particular attention needs to be paid to maintaining the balance of indicators in frail patients, such as the use of the lowest effective dose of anesthetics, the use of multimodal analgesia to reduce postoperative pain and minimize adverse reactions (*84,85*). Impaired skeletal muscle and skin function is partially associated with frailty during surgery, so soft tissue injury should be avoided during the procedure, and especially when moving the patient. In addition, manual handling and gel decompression support should be used to facilitate postural immobilization and avoid movement beyond the patient's normal range of motion (*79,86*). Furthermore, opioid analgesics should be used as appropriate during the perioperative period, and anticholinergic exposure should be minimized to reduce the risk of delirium (*84*). Reassessment after surgery is necessary to determine whether a frail patient needs intensive care or transfer to a specialized intensive care unit after surgery, and quality postoperative care and postoperative rehabilitation should be provided to the frail patient on a case-by-case basis (*87-89*). Patient-related postoperative complications, including delirium, deterioration of somatic function, falls, and pulmonary infections, need to be predicted, prevented, recognized, and managed in frail patients postoperatively (*90,91*). Early postoperative removal of unnecessary tubes and catheters, support for patients to sit up and move around, and assistance with regular orientation including the provision of hearing aids, eyeglasses, and nutritional support are needed (*79,92-94*). Obstacles to discharge for frail patients need to be recognized and resolved as early as possible in discharge plans, and discussing and recording the patient's anticipated rehabilitation and follow-up needs is important. More importantly, special attention needs to be paid to the post-discharge rehabilitation and care of older frail patients (*79*).

7. Management strategies for sarcopenia

Sarcopenia in elderly patients is primarily prevented during hospitalization with high-protein, multi-nutrient nutritional support and multi-component exercise strategies to prevent loss of muscle mass and maintain physical function and health-related QoL. As recommended by the ANZSSFR Expert Working Group, older patients identified as having sarcopenia or frailty should be assessed and tested by a dietician to determine appropriate nutritional support (*7*). According to the European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations, the basic energy requirement for inpatients should be 30 kcal/kg/day, and the basic requirement for protein should be 1.2 g/kg/day, adjusted according to the actual condition of the patient (*e.g.,* obesity or in critical condition) (*95*). A study has shown that high-protein supplementation was associated with reduced muscle loss and a lower incidence of malnutrition during hospital discharge (*96*). The ESPEN recommends that older adults, including those with sarcopenia and/or frailty, should undergo a multicomponent exercise program prescribed and supervised by a qualified health care professional as early as possible, including resistance, challenging balance, and functional training that can safely and effectively prevent functional decline during hospitalization (*96*). There is insufficient evidence to recommend any drug therapy for sarcopenia or frailty.

8. Conclusion

Inadequate awareness of frailty and sarcopenia in older patients by health care personnel can affect their ability to make appropriate surgical decisions for their patients. Overestimation of surgical risk may result in patients missing the best opportunity for surgery, while underestimation of surgical risk may expose patients to unnecessary risk. Screening for frailty may help predict postoperative complications and prognosis in elderly patients undergoing neurosurgery. In addition, screening patients for frailty and sarcopenia in a clinical setting can help formulate individualized care strategies to meet the complex needs of different patients. Unfortunately, there is a lack of standardized frailty assessment criteria, and the predictive efficacy of frailty prediction tools varies widely under the same conditions. Further research needs to be conducted on frailty assessment strategies in patients undergoing neurosurgery, and a multidisciplinary assessment involving surgeons, anesthesiologists, intensivists, and geriatricians should be conducted to formulate the most appropriate management strategies. Based on the findings of the current review, proactive interventions for elderly frail patients are likely to improve postoperative recovery and patient QoL, with promising real-world applications.

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Mini-Review

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Alzheimer's disease with frailty: Prevalence, screening, assessment, intervention strategies and challenges

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SUMMARY Alzheimer's disease (AD) is a neurodegenerative disorder that affects millions worldwide and is expected to surge in prevalence due to aging populations. Frailty, characterized by muscle function decline, becomes more prevalent with age, imposing substantial burdens on patients and caregivers. This paper aimed to comprehensively review the current literature on AD coupled with frailty, encompassing prevalence, screening, assessment, and treatment while delving into the field's challenges and future trajectories. Frailty and AD coexist in more than 30% of cases, with hazard ratios above 120% indicating a mutually detrimental association.Various screening tools have emerged for both frailty and AD, including the Fried Frailty Phenotype (FP), FRAIL scale, Edmonton Frailty Scale (EFS), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), and General Practitioner Assessment of Cognition (GPCOG). However, none has solidified its role as the definitive gold standard. The convergence of electronic health records and brain aging biomarkers heralds a new era in AD with frailty screening and assessment. In terms of intervention, non-pharmacological strategies spanning nutrition, horticulture, exercise, and social interaction, along with pharmacological approaches involving acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, and anti-amyloid beta-protein medications, constituted cornerstones for treating AD coupled with frailty. Technological interventions like repetitive transcranial magnetic stimulation (rTMS) also entered the fold. Notably, multi-domain non-pharmacological interventions wield considerable potential in enhancing cognition and mitigating disability. However, the long-term efficacy and safety of pharmacological interventions necessitate further validation. Diagnosing and managing AD with frailty present several daunting challenges, encompassing low rates of early co-diagnosis, limited clinical trial evidence, and scarce integrated, pioneering service delivery models. These challenges demand heightened attention through robust research and pragmatic implementation.

Keywords Alzheimer's disease, frailty, epidemic, screening, intervention, challenge

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, representing a neurodegenerative disorder characterized by a gradual onset and the progressive deterioration of cognitive and functional capacities. According to the 2018 Global Alzheimer's Disease Report by Alzheimer's Disease International (ADI), the worldwide population living with dementia exceeded 50 million individuals, with projections estimating a surge to 152 million by 2050 (*1*). Approximately 60–70% of those cases can be attributed to AD. Frailty emerges as a syndrome denoting heightened vulnerability in older adults, encompassing factors like co-morbidities such as hypertension, diabetes, and heart disease (*2*).

Recent investigations have highlighted a robust correlation between frailty and AD. In their study, Kojima *et al.* unveiled a staggering 31.9% prevalence of frailty in patients exhibiting mild to moderate AD. Moreover, frailty exhibited strong links to cognitive decline, functional disability, mortality, and various other adverse health outcomes (*3*). A comprehensive systematic review led by Grande *et al*. underscored that the risk of dementia development surpassed fivefold

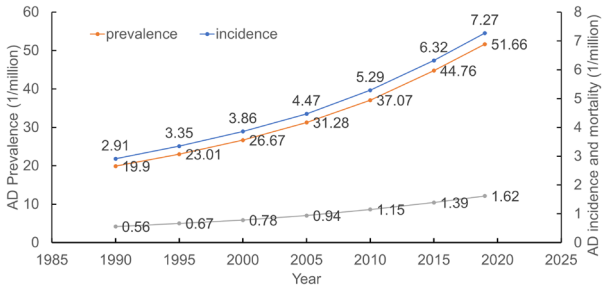

Figure 1. Epidemic of Alzheimer's disease (AD) from 1990-2019. Data source: *http://ghdx.healthdata.org/gbd-results-tool*

when cognitive impairment and frailty coexisted compared to individuals lacking either condition (*4*). The intersection of AD and frailty has rapidly evolved into a focal point of global research and preventative efforts, emerging as a significant public health concern.

This article encapsulates the present landscape concerning AD's prevalence, screening, and treatment in conjunction with frailty. As such, it offers a valuable reference for global prevention and management strategies in addressing the amalgamation of AD and frailty.

2. Epidemic situation of AD with frailty

The incidence, prevalence, and mortality of AD are on an escalating trajectory worldwide (*5*), as evidenced by the WHO's Global Burden of Disease (GBD) surveillance data (Figure 1). The prevalence of frailty escalates with advancing age and is distinctly influenced by socioeconomic disparities, with noticeably higher rates documented in low- and middle-income nations (*6*). The convergence of AD and heightened frailty substantially burden societal health. A comprehensive analysis of frailty prevalence in patients experiencing mild to moderate AD revealed a spectrum ranging from 11.1% to 50.0%, averaging 31.9% (*3*). Another systematic assessment focusing on frailty prevalence among dementia patients conducted in acute care environments observed rates spanning from 50.8% to 91.8%. In contrast, studies conducted in community-based residential settings indicated even higher prevalence rates. In such community residential settings, frailty prevalence spanned from 24.3% to 98.9% (*7*). Furthermore, an investigation encompassing older adults with limited cognitive capacity in Central Africa documented an estimated frailty prevalence of 64.9% (*8*). Employing the frailty index (FI), Heather *et al.* gauged frailty prevalence among participants in clinical trials targeting mild cognitive impairment (MCI) and dementia. the dementia trial noted a significantly higher rate of 48.6% (*9*). An additional retrospective evaluation, centering on patients aged 65 and older from two centers specializing in cognitive decline and dementia (CCDDs), disclosed that 40% of patients exhibited mild frailty. In contrast, 25% faced moderate to severe frailty. Intriguingly, the prevalence and severity of frailty exhibited a positive correlation with declining Mini-Mental State Examination (MMSE) scores and increasing age (*10*). Lee *et al.* assessed the prevalence of frailty within primary care settings among patients presenting memory complaints. Their findings showcased a frailty prevalence of 16% based on Fried's criteria and an elevated 48% according to the Clinical Frailty Scale (CFS). The collective findings of the aforementioned epidemiological investigations underscore the substantial prevalence of AD accompanied by frailty (*11*). Kasajima *et al.* harnessed a microsimulation methodology to forecast the prevalence and economic implications of dementia and frailty among the population aged 60 years and above in Japan from 2016 to 2043. Their projections anticipate an approximately 1.3-fold increase in frailty prevalence among individuals aged 75 and older by 2043. Alarming statistics reveal that nearly 29% of women aged 75 and above will grapple with dementia and frailty, precipitating an annual expenditure of $125 billion and $97 billion on dementia-related and frailty-related costs, respectively (*12*).

Conversely, multiple studies have established a substantial correlation between frailty and AD. An investigation into the interplay between frailty and dementia incidence within China unveiled that, over five years, the cumulative incidence of frailty coexisting with dementia markedly exceeded that of dementia without frailty. Different definitions of frailty yielded consistent results: 21.0% compared to 9.6%, 19.9% compared to 9.0%, and 22.8% compared to 8.9% (*13*). Cognitive capabilities among frail older adults generally register lower compared to their non-frail counterparts (*14*), with the occurrence of MCI 1.6 to 2.5 times more prevalent in the former group (*15,16*). Additionally, pre-frail subjects exhibited a higher prevalence of cognitive impairment than cognitively normal older adults, while the incidence of cognitive dysfunction was even greater among frail individuals than those who are pre-frail (*17*). Similar findings have been reported in several investigations of debilitating specialties, such as an investigation of the prevalence of MCI among patients with sarcopenia, which found that the prevalence of MCI among patients with sarcopenia was 20.5% (95% CI: 0.14–0.26) and that the overall adjusted ratio between MCI and sarcopenia was 1.46 (95% CI: 1.31–1.62). The prevalence of MCI was relatively high in patients with sarcopenia, and sarcopenia may be a risk factor for MCI (*18*). Furthermore, systematic evaluations have documented escalated instances of both debility and sarcopenia within dementia patients. A study targeting debility through the lens of swallowing quality of life (SwalQoL) underscored a noticeable escalation in frailty prevalence in tandem with declining cognitive status (*19*). Correspondingly, the prevalence of sarcopenia among individuals with dementia demonstrated an analogous elevation alongside cognitive deterioration (*20*).

3. Progress in screening and assessment of AD with frailty

3.1. Frailty screening tool

Globally, an array of assessment methods have emerged to facilitate routine frailty screening. Nevertheless, a universally recognized "gold standard" for frailty assessment remains elusive. The Fried Frailty Phenotype (FP), the FRAIL scale, and the Edmonton Frailty Scale (EFS) are among the more widely employed tools. The FP, introduced by Fried in 2001, comprises five criteria: weight loss, low physical activity, exhaustion, slowness, weakness (*21*). The FRAIL scale, devised by experts from the International Working Group on Nutrition, Health, and Ageing in 2008, incorporates the following five components: fatigue, resistance, ambulation, illness, and loss of weight (*22*). Another frequently utilized assessment tool, the EFS, was introduced by Rolfson *et al.* in 2006. It encompasses nine dimensions and eleven entries: cognition, general health status, self-reported health, functional independence, social support, polypharmacy, mood, continence, and functional performance (*23*). An appraisal by Han *et al.* regarding the consistency and applicability of these three scales for frailty screening among community-dwelling older adults revealed divergent outcomes. Notably, the EFS emerged as more suitable for comprehensively assessing frailty in this population, whereas the FP demonstrated greater efficacy than the FRAIL scale in gauging physical frailty (*24*). Another comparison conducted by Dent underscored certain limitations, such as the need for instrumental grip strength measurements in FP, potentially impeding its widespread use. Moreover, the FRAIL scale necessitated further validation efforts (*25*). Recent trends within the field signal a shift toward measurement tools integrated with electronic health records. Notable examples included the electronic frailty index (eFI) and the Hospital Frailty Risk Score (HFRS), both of which have demonstrated promising levels of differentiation in preliminary assessments (*26-28*).

3.2. Screening tools for cognitive impairment

Numerous cognitive assessment scales were employed both domestically and internationally within clinical contexts. Among these, MMSE stands out as the most prevalent, alongside other tools like the Montreal Cognitive Assessment Scale (MoCA), the Clock Drawing Test (CDT), and the General Practitioner Cognitive Functioning Assessment Gauge (GPCOG), among others (*29,30*). The MMSE, introduced by Folstein *et al.* in 1975, is particularly prominent due to its brevity and applicability across various subject profiles. The scale evaluates five domains: orientation, memory, attention, language, and visuospatial skills (*31*). Developed by Nasreddine *et al.* in Canada in 2005, the MoCA proves invaluable in swiftly screening for MCI. While the MoCA exhibits enhanced sensitivity towards MCI compared to the MMSE, it necessitates a higher literacy level due to its more intricate assessment content. This tool encompasses eight primary cognitive domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation (*32*). First introduced in 1989 for detecting structural dysfunctions, the CDT is lauded for its ease of administration, brevity (typically 1–3 minutes), and reduced susceptibility to factors like cultural disparities and educational levels. It delves into a broad spectrum of cognitive functions beyond spatial structural skills, encompassing visuospatial structural capacities, verbal memory, and executive functions. This test emerges as highly sensitive in screening early cognitive dysfunction. It tasks the patient with drawing a clock according to specific instructions, serving as a single-item assessment primarily targeting executive functions. It also evaluates cognitive domains such as visuospatial and executive capabilities, auditory-verbal skills, attentional focus, and structural functionality (*33*). Introduced in 2002, the GPCOG is tailored for application within primary care settings. The assessment comprises two components: a patient test and an informant survey. The patient test features six items: orientation, memory, attention, language, visuospatial skills, and executive function. The informant survey consists of 6 questions, generating scores of 9 out of 9 for the patient test and 6 out of 6 for the informant survey. Typically, administration takes less than 2 minutes (*34*) (Table 1). Recently, the Chinese Aging Marker Research Consortium has pioneered the exploration and proposal of brain aging biomarkers, striving to achieve a scientific measurement of biological age within the population. The Consortium has constructed markers spanning behavioral and functional realms, imaging parameters, and humoral indicators (*35*).

3.3. Developments in the evaluation of AD with frailty

Although frailty and AD are inextricably linked, current evaluation approaches primarily focus on isolated measures or translational analyses of each condition. For instance, a FI may be created by combining results from cognitive tests with activities of daily life. However, as revealed by Ward *et al.*, it is worth noting that the association between frailty and dementia risk was attenuated after certain early core dementia symptom factors were eliminated (*36*). This underscores the intricate relationship between these factors. Engvig *et al.* adopted a data-driven approach to evaluating health deficits, aiming to enhance the predictive accuracy of the FI concerning both current cognitive status and the likelihood of future dementia. This effort brings to light the potential shortcomings of the traditional FI when applied to dementia risk assessment (*37*). Li *et al*., on the other hand, devised a nomogram integrating risk factors

Table 1. Frailty and AD screening instruments

Field	Name	Items	Type and scope of scoring	Evaluation method	Advantage	Shortcomings
Frailty	FP	weight loss, low physical activity, exhaustion,slowness, weakness	0–5 points, ≥ 3 points indicates frailty	Face to face, professional equipment required	TUGT, grip strength, and other objective markers are included, and it is also more sensitive to physical weakness. It is straightforward and simple to use.	Only takes into account physical dimension. ignores additional contributing elements like emotion and cognition.
Frailty	FRAIL	fatigue, resistance, ambulation, illness, loss of weight	0–5 points, ≥ 3 points indicates frailty	self-reporting	straightforward and simple to use; contains both subjective and objective metrics.	Only takes into account physical dimension. Due to cognitive impairment, senior persons may have an erroneous assessment of their physical state.
Frailty	EFS	cognition; general health status: self-reported health: functional independence: social support; polypharmacy; mood; continence; and functional performance	0–17 points, ≥ 5 indicates frailty	Face to face, professional training required	Several physiological and disease-related indicators are present; can be used to assess the effects of interventions.	The examination is rather intricate and is only applicable to hospital circumstances; Some indicators might be affected by illnesses.
Cognitive Disorder	MMSE	orientation, memory, attention, language, and visuospatial skills	0–30, < 24 indicates frailty	Face to face, professional training required	The diagnostic sensitivity and specificity for dementia are respectively 85% and 90%; relatively valuable for identifying AD.	False negative or false positive findings are noticeable and are dependent on the subject's education level; The questions are easy. There is a ceiling effect, which lowers the sensitivity of detecting MCI.
Cognitive Disorder	MoCA	visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation	0–30, ≥ 26 indicates normal cognitive function;	Face to face, professional training required	The specificity for detecting MCI is decent, with sensitivity for moderate AD and MCI being 90% and 100%, respectively.	The inquiries are time-consuming and quite challenging; many nations do not have a normative understanding of language and cultural variations.
Cognitive Disorder	CDT	Draw a closed circle, the position of the numbers is correct, all 12 numbers are not missing, and the position of the minute and hour hands is correct.	0–4 points, scoring 3–4 points indicate normal cognitive level	Face to face, professional training required	The highest sensitivity and specificity for diagnosing cognitive disorders are 97.9% and 94.2%, respectively; the method is simple to use and unaffected by cultural differences, educational attainment, or other variables.	Being unable to identify a patient's precise type of cognitive dysfunction
Cognitive Disorder	GPCOG	orientation, memory, attention, language, visuospatial skills, and executive function	0-9 points, ≥ 5 indicates normal	Face to face, professional training required	Simple to use; high reliability and validity; the Chinese version's sensitivity and specificity for detecting AD are up to 98.08% and 91.94%; It is appropriate for AD screening at the community level	When screening for MCI, there is still a chance of missing diagnosis or misdiagnosis, hence it is required to integrate different scales for screening.

Abbreviations: AD, Alzheimer's disease; CDT, Clock Drawing Test; EFS, Edmonton Frailty Scale; FP, The Fried Frailty Phenotype; GPCOG , the General Practitioner Cognitive Functioning Assessment Gauge; MCI, mild cognitive impairment ; MMSE, Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment Scale.

for frailty within the elderly Chinese AD population. Their findings elucidated that factors such as older age, irregular exercise habits, substantial cognitive decline, and insufficient social support played pivotal roles in contributing to physical frailty among AD patients. The constructed nomogram exhibited a C-index of 0.884, indicative of robust differentiation and calibration capabilities. These insights collectively underscore the intricate relationship between frailty and AD, further emphasizing the need for more refined assessment tools to capture their complex interplay (*38*).

4. The improvement of AD with frailty therapy and intervention

4.1. Non-pharmacological treatment

Nutrition, horticultural treatment, physical activity, and social interaction are just a few of the disciplines that are combined in non-pharmacological therapies. A study conducted in Hyogo Prefecture, Japan, introduced a multifactorial Frailty Prevention Curriculum (FPC) within the community. This curriculum encompassed resistance exercise, nutritional education, and a psychosocial program overseen by trained geriatric professionals. Encouragingly, results revealed that older adults participating in the FPC exhibited significantly diminished risks of functional disability, notably attributable to dementia, over a 6.8-year observation period (*39*). A separate investigation undertaken in a New Zealand community randomized pre-frail older adults into distinct class combinations: a nutrition education and cooking class (SC), a strength and balance exercise program (SAYGO), a combined program (COMBINED), or a social activity program (CONTROL). While no significant disparities were initially observed among the four groups based on Fried frailty scores during the 2-year tracking phase, the SAYGO group demonstrated a noteworthy improvement compared to the control group at the 6-month mark (*40*). Other studies have delved into the impacts of horticultural therapy on physical functionality and psychological well-being among older adults. Horticultural therapy dramatically improves upper extremity flexibility and aerobic endurance in elderly cancer patients, according to this study. Additionally, it promotes subjective social relationships, overall quality of life, and emotional well-being (*41*). Salzman *et al.* systematically evaluated the effects of multidomain interventions on cognitive functioning among MCI patients. This examination, encompassing 28 randomized controlled trials (RCTs), unveiled that multidomain interventions yielded substantial enhancements in overall cognition, executive functions, memory, and verbal fluency. However, the study observed no significant differences in attention and processing speed. The multidomain intervention also correlated with improved scores on specific cognitive assessments like the MMSE, Category Verbal Fluency Test, Trail Making Test-B, and Wechsler Memory Scale-Logical Memory I and II. Ultimately, the study deduced that short-term multidomain interventions (spanning less than one year) can ameliorate cognitive functioning in individuals with MCI. However, additional research is necessary to ascertain the ideal intervention duration (*42*).

4.2. Drugs and physical therapy

Acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, anti-amyloid -protein (A) medications, and novel targeted therapeutic agents were all thoroughly examined in the World Alzheimer Report of 2022 (*43*). While AChEIs and NMDA receptor antagonists exhibit cognitive function enhancement, they are accompanied by increased adverse effects. Aβ Drugs show the ability to delay cognitive aging, but stronger proof is still needed to support this claim. Novel targeted therapies, although promising, necessitate further studies to validate their safety and efficacy (*44,45*). Seibert *et al.* contributed to the discourse by investigating the efficacy and safety of pharmacotherapy in older AD patients grappling with debilitating or impaired function. Their findings indicated that AChEIs marginally improved cognitive function yet exhibited no substantial effect on functional status or behavioral and psychological symptoms (BPSD). Antidepressants demonstrated limited improvement in depressive symptoms. Antipsychotics and anticonvulsants exhibited mild effects on select BPSD facets, albeit accompanied by heightened adverse effects (*46*). Thapaliya *et al.* conducted a longitudinal cohort study evaluating medication usage among older women in Australia between 2003 and 2015. They observed that women with dementia residing in nursing homes displayed elevated rates of medication reviews (MR), although the usage remained below 50% (*47*). Wei *et al.* embarked on a systematic evaluation and Bayesian network meta-analysis to compare the effectiveness of repetitive transcranial magnetic stimulation (rTMS) with medication among AD patients. Their investigation highlighted rTMS as superior to placebo and multiple medications in enhancing cognitive function while exhibiting the lowest incidence of adverse effects (*48*). Okahara *et al.* delved into the effects of the multi-component drug "ginseng nourishing broth" (Ninjin'yoeito) on debilitating symptoms in patients with MCI and mild AD. Their research demonstrated how Ninjin'yoeito's anorexia early on improved anorexia scores on the Neuropsychiatric Symptoms Scale. After 24 weeks, there was no sign of frailty and significant improvements in the Cardiovascular Health Study scores were seen. Moreover, scores on the fatigue

Table 2. Treatment type and effectiveness of Alzheimer's disease (AD) accompanied by frailty

Types of Intervention	Content of Intervention	Effectivness of Intervention
Non-pharmacological interventions	Program to prevent frailty that takes a multifaceted approach that incorporates resistance training, nutrition education, and psychosocial interventions	Functional disability risk was significantly lower (HR = 0.53, 95% CI: 0.38–0.75), notably for functional disability brought on by dementia (HR = 0.47, 95% CI: 0.25–0.86).
	Combining lessons, such as classes on nutrition education and cooking, classes on strength and balance, and both	At six months, the SAYGO group outperformed the Friend control group (-0404, 95% CI: -068 to -0123).
	Horticultural therapy	Improvement in aerobic endurance (SMD = 0.79, 95% CI: 0.41–1.16) and upper body flexibility (SMD = 0.26, 95% CI: 0.03–0.50) as well as an improvement in general quality of life.
	Multiple exercise or cognitive therapies, dietary supplements, cognitive, physical, and social activities, joint cognitive training with transcranial direct current stimulation, *etc*. are examples of multidomain interventions	Among other things, there was a substantial improvement in executive function (SMD = 0.20; 95% CI: 0.04–0.36) , memory (SMD = 0.29; 95% CI: 0.14–0.45), verbal fluency (SMD = 0.30; 95% CI: 0.12–0.49), and global cognition (SMD = 0.41; 95% CI: 0.23–0.59).
Pharmacological interventions	Acetylcholinesterase Inhibitors (AChEIs)	Donepezil, rivastigmine, and galantamine are cholinesterase inhibitors that are cognitively beneficial in mild to severe Alzheimer's disease (Class A).
	Memantine	In patients with mild to moderate Alzheimer's disease, memantine is cognitively successful (Class A), and combination therapy with cholinesterase inhibitors may be helpful (Class B).
	Anti-amyloid-beta (Aβ) drugs	Particularly Aducanumab and Lecanemab, anti-A monoclonal antibodies significantly enhanced cognitive and biomarker outcomes. The use of these medications alone is unlikely to fundamentally alter the development of AD in a clinically relevant way because the cognitive effects were minor. Second, these medications significantly up the chance of adverse effects such headaches and cerebral edema (ARIA-E).

visual analog scale significantly increased (*49*) (Table 2).

4.3. Innovative intervention models

Suharya's research focuses on combining medical and social care techniques to provide post-diagnosis support to people in Korea who are dealing with cognitive impairment (*50*). Three different service categories are identified in the article: *i*) A year-long, individualized support system is provided by specialists as part of the Post-Diagnostic Support Program for Cognitive Impairment (PDS). This all-encompassing help entails providing knowledge, instruction, psychological assistance, encouraging social activity, and assisting with legal planning. *ii*) Individuals and families dealing with cognitive disorders can get comprehensive help from the Community Cognitive Disability Centers (CDCs). Comprehensive assessments, counseling, therapy, childcare, in-home care, and emergency response are all included in these services. *iii*) Specialized Cognitive Disorder Hospitals (SDHs) focus on providing patients with cognitive impairments with specialized medical care. Their services span medication administration, surgical interventions, rehabilitation, and inpatient care. The authors underscore that these services collectively contribute to delaying cognitive decline, mitigating social expenses and hospitalization rates, curbing complications and mortality, and enhancing the overall quality and safety of care, among other benefits. Lorimer provides insights into the Scottish model of care, which includes aspects of diagnosis, post-diagnostic support, community assistance involving the coordination of medical and social agencies, and provision for hospital and institutional care (*51*). Oliveira's work focuses on Brazilian reforms and innovative approaches to diagnosing and treating cognitive disorders within the primary health care system. Notably, the primary health care system offers access to both pharmacological and non-pharmacological treatments, incorporating cognitive stimulation, psychosocial support, and exercise interventions. Specialized memory clinics have been established to conduct multidisciplinary assessments and management with primary health care teams. Moreover, primary health care workers receive training and support to enhance their knowledge and competence in addressing cognitive impairment and facilitating communication with specialists. Additionally, digital technologies, such as teleconsultation, electronic health records, and mobile applications, have been leveraged to improve accessibility and efficiency in diagnosing and treating cognitive impairment (*52*).

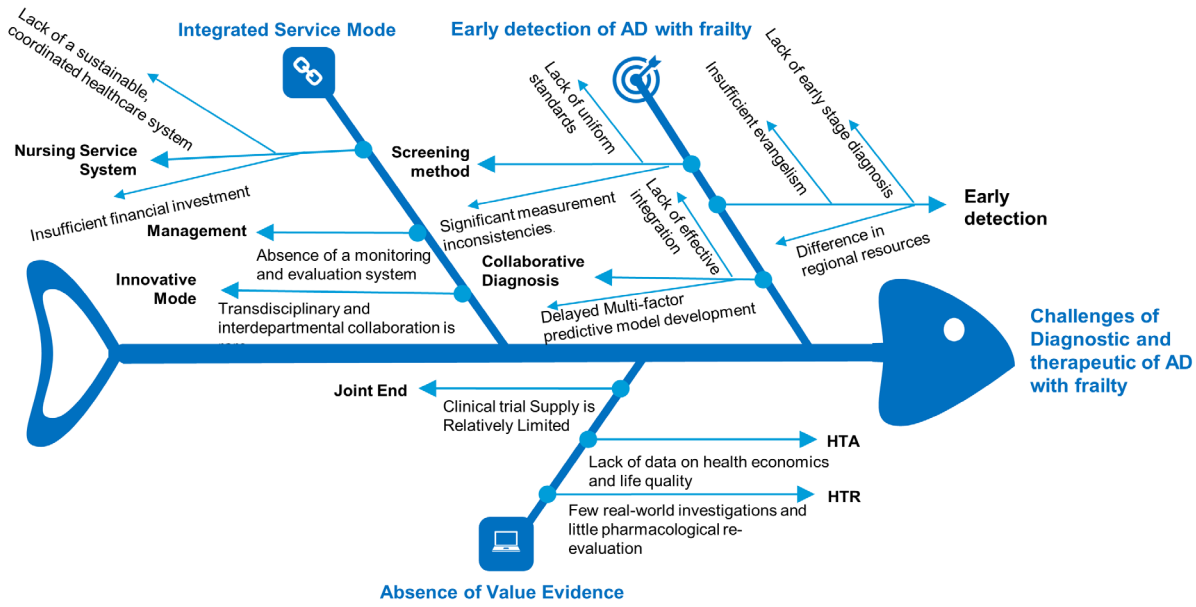

Figure 2. Diagnostic and therapeutic challenges for Alzheimer's disease (AD) with frailty. HTA, health technology assessment; HTR, health technology reassessment.

5. Diagnostic and therapeutic problems for AD with frailty

5.1. Improving the early detection of AD with frailty

Recent studies have gradually shown the higher frequency of frailty and AD, showing the complex interactions between the two. Within the current clinical intervention paradigms, this emergent element has now taken the lead: *i*) The key to addressing the urgent issue is early detection of AD during its asymptomatic and severe stages. It is crucial to find solutions to the problems caused by varying diagnostic standards, resource constraints, cultural differences, and ethical considerations in various countries. *ii*) Because there aren't many standardized tests available, current screening techniques suffer from significant measurement inconsistencies. *iii*) The integration of current diagnostics is still far from perfect. Although they are in use, predictive models often struggle with small sample numbers and frequently overlook potential confounding factors including patient history and the more recent contributions of biomarkers, imaging methods, and genetic testing technologies. These factors all work together to reduce the accuracy, dependability, and accessibility of diagnostic information. Addressing these issues becomes crucial as the therapeutic landscape develops.

5.2. The value of therapies and drugs for AD with debilitation are not supported by clinical trial

Clinical trials for senior patients with AD who exhibit frailty or functional impairment are noticeably lacking at the moment. In addition, there is a dearth of thorough evaluation data that considers factors like quality of life, financial impact, and social benefits for both patients and caregivers. Improvements in biological diagnostic accuracy, dependability, and accessibility of recently produced medications are also necessary. The need to increase the body of research pertaining to the cost-effectiveness, adherence, and safety of routine medication injection delivery is also widely acknowledged. The fact that just a small portion of drug use has been reviewed is notable and emphasizes the pressing need for stronger real-world evidence to demonstrate the effectiveness of these therapies.

5.3. To be developed: Integrated AD with frailty service model

Frailty and AD are serious public health issues that have an effect on both families and society. However, it is still clear that there is a lack of an egalitarian, sustainable, integrated, and high-quality care delivery system. The lack of specialized policies and uniform guidelines makes this shortfall even worse, which causes an insufficient allocation of human, material, and financial resources, particularly for preventative treatments during the pre-AD phase. The continued improvement of care service quality and efficacy is negatively impacted by the absence of efficient monitoring and evaluation systems at the managerial level. Another major obstacle is the insufficient support for cross-sectoral and interdisciplinary collaboration and coordination. This lack of cooperation prevents the field from spreading innovative concepts and outstanding practices. Consequently, it is necessary to to provide a comprehensive service model to handle this task (Figure 2).

6. Conclusion

Due to the significant and rising prevalence of AD and frailty, this situation poses a serious public health challenge that calls for preventative, regulatory, and therapeutic approaches. Evidently, there is still a sizable gap in the areas of screening, assessment, therapy, and intervention for people coping with the combination of frailty and AD. This unmet demand emphasizes the urgent need for more resources and ground-breaking solutions to be swiftly deployed.

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Review

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Association between sarcopenia with incident cardio-cerebrovascular disease: A systematic review and meta-analysis

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SUMMARY Sarcopenia is an age-associated skeletal muscle disease characterized by the progressive loss of muscle mass and function. The objective of this systematic review and meta-analysis was to evaluate the associations between sarcopenia and cardio-cerebrovascular disease (CCVD). A comprehensive search of the PubMed/Medline, Embase, Web of Science, Scopus, and Cochrane Library databases was conducted from their inception to April 1st, 2023. A total of eight cross-sectional studies involving 63,738,162 participants met the inclusion criteria. Pooled estimates of odds ratios (ORs) were calculated using random-effects models. The findings demonstrated a significant association between sarcopenia and an increased risk of CCVD (OR: 1.33, 95% CI: 1.18 - 1.50, I^2 = 1%; $p < 0.001$). Subgroup analyses indicated that sarcopenia was associated with a 1.67-fold increase in the risk of stroke and a 1.31-fold increase in the risk of CVD. Four studies included in this review examined the association between sarcopenic obesity and the risk of CCVD, and the results revealed that sarcopenic obesity was associated with a higher risk of CCVD (OR: 1.64, 95% CI: 1.08 - 2.49, I^2 = 69%; $p < 0.001$). Meta-regressions and sensitivity analyses consistently supported the robustness of the overall findings. In conclusion, sarcopenia and sarcopenic obesity are significantly associated with an elevated risk of developing CCVD. However, further prospective cohort studies are warranted to validate this relationship while controlling for confounding factors.

Keywords Sarcopenia; cardio-cerebrovascular disease risk; meta-analysis.

1. Introduction

Sarcopenia is an age-associated skeletal muscle disease characterized by the progressive loss of muscle mass and function. It has been consistently linked to adverse functional and health outcomes, including frailty, falls, nutritional deficiencies, and increased mortality rates (*1*). The prevalence of sarcopenia is heavily influenced by the criteria used for its definition and the measurement tools employed to assess its markers. Different definitions yield varying prevalence rates, providing us with a range of estimates. For instance, the European Working Group on Sarcopenia in Older People criterion suggests a prevalence of around 5%, while the International Working Group on Sarcopenia criteria indicate a higher estimate of about 17%. However, even within these definitions, the prevalence values can vary significantly based on the specific tools utilized to evaluate muscle mass, strength, and physical performance. To illustrate this, the prevalence values can range from as low as 1% to as high as 7% for muscle mass, 1% to 12% for strength, and even span from 0% to 22% for physical performance, respectively (*1*). Among specific populations, the prevalence of sarcopenia is reported to be between 4% and 33% in long-term care settings (*2*) and approximately 14.7% in hospitalized elderly patients (*3*). Moreover, the prevalence of sarcopenia varies across different regions. In Oceania, for example, the reported prevalence ranges from 1% to 40%. In South America, it ranges from 13% to 35%, while in Europe, the prevalence is around 1%. Importantly, sarcopenia frequently coexists with other medical conditions, such as cardiovascular disease (31.4% prevalence) (*4*), chronic obstructive pulmonary disease (COPD) patients (27.5% prevalence) (*5*), heart failure patients (34% prevalence) (*6*), stroke patients (42% prevalence) (*7*), and diabetes (18% prevalence) (*8*). These high rates of comorbidity emphasize the clinical significance of sarcopenia in various disease contexts.

The increasing global aging population and the high

prevalence of sarcopenia have positioned sarcopenia as a focal point of interest within geriatric research and clinical practice. Various sociodemographic, lifestyle, and behavioral factors have been found to be significantly associated with sarcopenia among older adults. These factors include age, marital status, disability in activities of daily living, underweight status, smoking, physical inactivity, risk of malnutrition, sleep duration (either long or short), living alone, presence of diabetes, cognitive impairment, heart diseases, respiratory diseases, osteoporosis, osteoarthritis, depression, history of falls, anorexia, and anemia (*9*). These associations highlight the multifactorial nature of sarcopenia and underscore the need for comprehensive assessment and management strategies in addressing this condition.

Except for the well-established increased risks of frailty, falls, nutritional status, and mortality, emerging evidence suggests that sarcopenia may also contribute to an elevated risk of cardio-cerebrovascular disease (CCVD). CCVD, recognized as the leading global cause of mortality, arises from a complex interplay of various factors (*11*). Investigating the associations between sarcopenia and CCVD, particularly in the elderly population, holds significant relevance. To address this knowledge gap, we conducted a rigorous systematic review, meta-analysis, and synthesis of available published research. This study aims to provide an insightful overview of the association between sarcopenia and CCVD, enabling a better understanding of this important clinical relationship.

2. Materials and Methods

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (*12*). The study protocol was registered in the International Prospective Register of Systematic Reviews Database (PROSPERO) under the registration number CRD42023426047.

2.1. Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (1) observational studies, including case-control studies, cohort studies, and cross-sectional studies; (2) studies investigating the relationship between sarcopenia and the risk of CCVD (cardiovascular disease (CVD) and stroke); (3) studies reporting the association between sarcopenia and CCVD using measures such as odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs); (4) original articles published in the English language. Exclusion criteria encompassed: 1) nonhuman studies; 2) clinical trials or experimental studies; 3) studies that did not present primary data analyses (*e.g.*, letters, editorials, or narrative reviews); and 4) studies lacking clear methods for data extraction, including ORs, RRs, or HRs.

2.2. Literature search and selection

All records identified in the initial search underwent an independent screening for relevance by two reviewers (Fang M and Liu CH), starting from the titles, abstracts, and full texts. Disagreements were arbitrated by a third reviewer (Guo L). Relevant literature was systematically searched in multiple literature databases, including PubMed/Medline, Embase, Web of Science, Scopus, and the Cochrane Library, from inception to April 1st, 2023. The search terms employed a combination of free-text terms and controlled vocabulary pertaining to sarcopenia and CCVD. The complete search strategy is available in Table S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

Following the removal of duplicates, two researchers (Liu Y and Tang G) independently reviewed the titles of the remaining studies. After further elimination of irrelevant articles, they proceeded to evaluate the abstracts of the remaining studies. Subsequently, they assessed the full texts of the remaining studies, excluding those that did not meet the inclusion criteria. Disagreements were resolved through consensus. The same authors conducted the full-text screening to determine the final selection.

2.3. Data extraction

Two independent researchers (Fang M and Liu CH) utilized a standardized form to extract data from the included studies (an example of the data extraction form is provided in the supplementary materials, Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). The following data points were extracted: (1) first author's name; (2) year of publication; (3) study design; (4) study location; (5) age range and sex distribution; (6) sample size; (7) diagnostic method of sarcopenia and sarcopenic obesity; (9) outcome measures, including CVD and stroke; CVD was defined using the International Classification of Diseases (ICD), 10th Revision (ICD-10, CD-10 code 053-075) (*13*). (10) reported risks of CCVD in relation to sarcopenia (including ORs, RRs, HRs, and 95% CIs).

The effect sizes representing the most comprehensive adjustment for potential confounders were extracted. In studies with different exposure or disease subgroups, data from distinct subgroups was pooled using a fixed-effects model. In cases where an outcome of interest was reported without providing estimates, the corresponding article's author was contacted for further information. Any discrepancies or disagreements regarding data extraction were resolved through discussion and, if necessary, by reviewing the original data with the involvement of a third researcher (Guo L).

2.4. Quality assessment

The quality assessment of the included studies was conducted independently by two researchers (Fang M and Tang G) using the Newcastle-Ottawa Scale (NOS) (*14*). The NOS checklist consists of three sections: selection, comparability, and outcome. Each section can be awarded a maximum of four, two, and three points, respectively. Based on the NOS criteria, studies were categorized as having poor quality (1-3 points), fair quality (4-6 points), or high quality (7-9 points).

2.5. Data synthesis and statistical analyses

All statistical analyses were performed using R software (version 3.4.0; R: The R-Project for Statistical Computing, Vienna, Austria). The primary outcome of this meta-analysis was the association between sarcopenia and CCVD risk, evaluated using a common measure of association: ORs for cross-sectional studies. In cases where ORs were not reported, we included RRs and HRs as proxies for ORs in the pooled analysis. This is because when event rates are low, ORs, HRs, and RRs tend to approximate one another.

Heterogeneity was assessed using the Q test (*15*) and I2 score (*16*), quantifying the extent of heterogeneity. Random-effects models were utilized to calculate pooled effect sizes and test the significance of deviations from zero ($P < 0.05$, 2-tailed). Additionally, subgroup analyses and meta-regressions were conducted to analyze the sources of heterogeneity. Subgroup analyses using the random-effect models were conducted based on the following factors: sample size (< 5,000 or > 5,000), country (Korea or China), and outcomes (CVD or stroke). Furthermore, sensitivity analyses were conducted to assess the stability of the results by excluding each study individually and recalculating the combined effect size based on the remaining studies. To evaluate publication bias among the included articles, funnel plots, Egger's test, and the trim-and-fill method were employed in the current meta-analysis. A *P*-value less than 0.05 indicated the presence of potential small-study effects.

3. Results

3.1. Study selection

A total of 1,241 articles were identified through the aforementioned database search. In the comprehensive literature search, 863 relevant articles were yielded when duplications were excluded. After removing duplicates, the comprehensive literature search yielded 39 relevant articles. Following a thorough examination of the full texts, 21 records were excluded, resulting in the inclusion of eight studies for our meta-analysis. No additional eligible articles were found through the assessment of reference lists (Figure 1).

3.2. Study and patient characteristics

As shown in Table S3 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*), the eight included studies were published between 2005 and 2022 and encompassed a total of 63,738,162 human participants (*17-24*). The mean age of the participants was 54 years, with a majority being women (57%). The studies were conducted in Asia, with six originating from Korean institutes and the remaining two from China.

Among the eight studies, sarcopenia was investigated as an exposure variable, while four of them also examined sarcopenic obesity as an exposure variable. The most common CCVD reported outcomes were CVD ($n = 8$), followed by stroke ($n = 2$). The study-specific and maximally adjusted ORs were extracted from the selected studies and pooled for the meta-analysis.

3.3. Methodological quality

To assess the quality of all studies, the NOS score was employed. Scores ranging from 0 to 3, 4 to 6, and 7 to 9 were considered indicative of low, fair, and high quality, respectively. Among the eight studies, all attained a high-quality rating with an average NOS score of 8, indicating good methodological quality (Table S4, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

3.4. Association between sarcopenia and CCVD risk

The association between sarcopenia and the risk of CCVD was assessed in all eight eligible studies. The meta-analysis revealed that sarcopenia was significantly associated with an increased risk of CCVD (OR: 1.33, 95% CI: 1.18 - 1.50, $I^2 = 1\%$; $p < 0.001$; Figure 2) using a random effect model.

3.5. Subgroup analysis of sarcopenia and CCVD

Subgroup analyses were conducted based on various factors, including sample size (> 5,000 or < 5,000), country (Korea or China), and disease (CVD or stroke), to investigate the impact of different population characteristics on the relationship between sarcopenia and the risk of CCVD. The results of the subgroup analysis for sarcopenia and CCVD risk are summarized in Figure 3.

In studies with large sample sizes (> 5,000), the pooled OR for CCVD risk was 1.36 (95% CI: 1.14 - 1.61, $p < 0.001$). However, no significant association was found between sarcopenia and CCVD (OR = 1.36, 95% CI: 0.99 - 1.87) in studies with small sample sizes (< 5,000). Additionally, we found that sarcopenia increased the risk of CCVD in Korea (OR = 1.15, 95% CI = 1.03 -

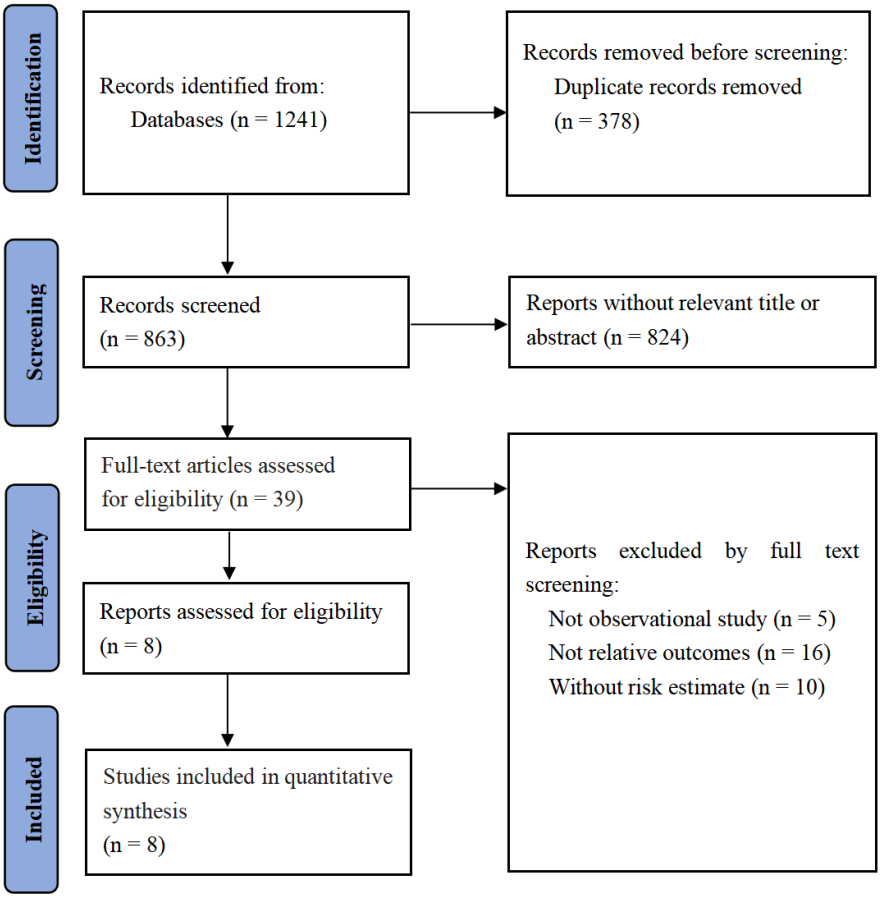

Figure 1. Literature search flow chart. Flowchart of the literature search and selection for systematic review and neta-analysis.

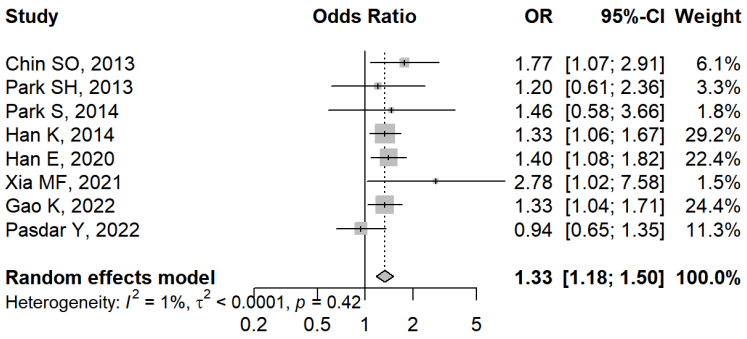

Figure 2. Forest plot of the association between sarcopenia and cardio-cerebrovascular disease. Forest plot for the meta-analysis examining the overall association between sarcopenia and cardiovascular disease (OR and 95% CIs) using a random effects model. OR, odds ratio; CI, confidence interval.

1.28, n = 6) but not in China (OR: 1.63, 95% CI: 0.85 - 3.01, n = 2). Moreover, participants with sarcopenia had a higher risk of stroke (OR = 1.67, 95% CI = 1.18 - 2.37, p = 0.004) compared to CVD (OR = 1.31, 95% CI = 1.14 - 1.49, p < 0.001).

3.6. Association between sarcopenia obesity and CCVD risk

Four studies reported an association between sarcopenic obesity and the risk of CCVD. The meta-analysis demonstrated that the presence of sarcopenic obesity was significantly associated with an increased risk of CCVD (OR: 1.64, 95% CI: 1.08 - 2.49, I^2 = 69%; p < 0.001; Figure 4) using a random effect model.

3.7. Meta-regression and sensitivity analyses

A meta-regression analysis was performed to explore potential sources of heterogeneity. However, the meta-

Subgroup	No. of reports	Odds Ratio (95% CI)	Odds Ratio (95% CI)	*P* for test	I^2 (%)	*P* for heterogeneity
Overall	8		1.33 (1.18 - 1.50)	<0.001	1%	0.42
Sample size						
>5000	4		1.36 (1.14 - 1.61)	0.06	33%	0.971
<5000	4		1.36 (0.99 - 1.87)	<0.001	41%	0.081
Country						
Korea	6		1.15 (1.03 - 1.28)	<0.001	0%	0.872
China	2		1.63 (0.85 - 3.01)	0.138	48%	0.162
Disease						
CVD	8		1.31 (1.14 - 1.49)	<0.001	4%	0.397
Stroke	2		1.67 (1.18 - 2.37)	0.004	0%	0.99

Figure 3. Subgroup analysis of the association between sarcopenia and cardio-cerebrovascular disease.

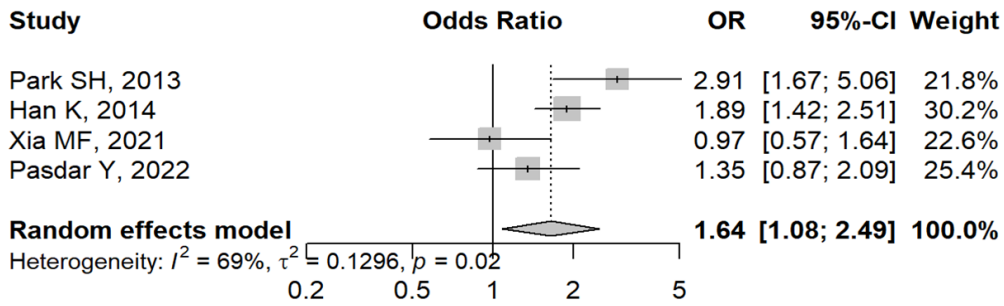

Figure 4. Forest plot of the association between sarcopenic obesity and cardio-cerebrovascular disease. Forest plot for the meta-analysis examining the overall association between sarcopenic obesity and cardiovascular disease (OR and 95% CIs) using a random effects model. OR, odds ratio; CI, confidence interval.

regression analysis of publication year, age, and sample size did not identify any obvious contributors to the heterogeneity (Table S5, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

To ensure the robustness of our findings and account for the significant heterogeneity observed among the included studies, sensitivity analyses were performed using random-effects models. These analyses involved sequentially excluding each study from the meta-analysis and examining the impact on the combined OR. The sensitivity analyses indicated no significant variation in the combined OR ($P > 0.05$), suggesting the reliability of our results (Figures. 5A and 5B).

3.8. Publication bias

In the current meta-analysis, publication bias among the included articles was assessed using a funnel plot, Egger's test, and the trim and fill method. The funnel plot displayed an asymmetric distribution (Figure S1, A, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). However, Egger's test did not suggest the presence of publication bias ($p = 0.463$). The trim-and-fill analysis indicated that two studies might be missing (Figure S1, B, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). Nevertheless, after adjusting for these potentially missing studies using the trim-and-fill method, the significance of the effect sizes was attenuated but remained statistically significant (OR = 1.29; 95% CI = 1.14 - 1.45).

4. Discussion

4.1. Summary of main results

In this systematic review and meta-analysis, we conducted a comprehensive evaluation of eight studies involving a total of 63,738,162 participants to investigate the association between sarcopenia and incident CCVD. Our findings indicate that sarcopenia is significantly associated with an increased risk of cardiovascular disease and cerebrovascular disease. To the best of our knowledge, this is the first systematic review and meta-analysis specifically examining the relationship between sarcopenia and CCVD.

4.2. Comparison between this and other meta-analyses

Several mechanisms, including inflammatory cell

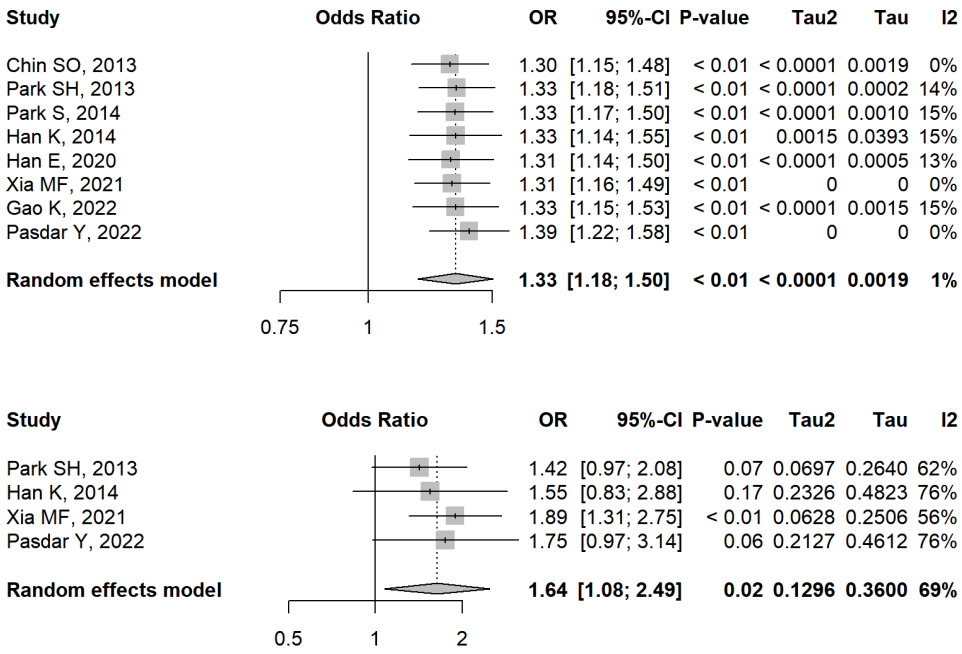

Figure 5. Sensitivity analysis. (A) Association between sarcopenic and CCVD. (B) Association between sarcopenic obesity and CCVD. Sensitivity analysis showed that there was no significant variation in the combined OR after omitting any one of the studies.

infiltration, hormonal dysfunction, impaired capillary blood flow, and reduced repair and regeneration capacity, have been associated with sarcopenia and may explain its relationship with CCVD (*25,26*). Considering the involvement of inflammation in the development of sarcopenia, recent studies have explored the association between the dietary inflammatory index and sarcopenia, highlighting its potential as a biomarker (*27*). Further investigations are needed to determine whether targeting the dietary inflammatory index could be a potential therapeutic approach for sarcopenia.

As an age-related musculoskeletal disorder, previous meta-analyses have primarily centered on investigating the impact of sarcopenia on frailty, falls (*28*) and mortality (*29*) in older populations and suggested that sarcopenia is associated with several harmful outcomes. This focus is reasonable because reduced muscle mass and the function of sarcopenia can easily contribute to falls and the development of frailty. Furthermore, meta-analyses of observational studies have demonstrated that sarcopenia is not only associated with an increased risk of metabolic syndrome and diabetes (*30*), but also other neurological diseases, such as depression, cognitive impairment, and dysphagia in the general population (*31*).

Sarcopenia, as a comorbid condition, is highly prevalent in numerous non-communicable diseases and has been shown to have a negative impact on the prognosis of affected patients. Among patients with cirrhosis, a meta-analysis has revealed a strong and independent association between sarcopenia and a higher risk of hepatic encephalopathy (*24*)(*32*) and mortality (*33*). Similarly, in septic patients, sarcopenia has been associated with increased mortality risk at 3-6 months and 1 year (*34*). Among dialysis patients, sarcopenia is significantly associated with higher mortality risk and cardiovascular events (*35*). Additionally, in patients undergoing mechanical ventilation, sarcopenia is related to increased mortality, a longer duration of mechanical ventilation, and a prolonged hospital stay (*36*). Therefore, sarcopenia imposes a substantial burden not only on society but also on public health.

Our meta-analysis yielded a significant finding, indicating a 33% higher risk of CCVD in patients with sarcopenia compared to those without sarcopenia. This relationship was particularly prominent in the subgroup analysis with a sample size larger than 5000. Furthermore, subgroup analyses examining different outcomes revealed that sarcopenia is associated with a 1.67-fold increase in the risk of stroke and a 1.31-fold increase in the risk of CVD. Moreover, when considering different countries, the subgroup analysis indicated that sarcopenia is associated with an increased risk of developing CCVD in Korean populations. However, this association was not observed in Chinese populations. To obtain a comprehensive understanding of sarcopenia and its impact on CCVD risk, future studies should investigate sarcopenia across diverse countries.

Age-related changes in body composition, such as an increase in fat mass and a loss of muscle mass, or sarcopenia, contribute to the high prevalence of sarcopenic obesity among the elderly. Previous studies have suggested the existence of a vicious cycle between fat accumulation and skeletal muscle loss, as increased visceral fat leads to inflammation, which in turn contributes to the development of sarcopenia

(*37*). In our meta-analysis, we have investigated the association between sarcopenic obesity and CCVD. The findings revealed that the risk of CCVD associated with sarcopenic obesity (1.64 times) was higher than the risk of CCVD associated with sarcopenia alone (1.33 times). This indicates that both sarcopenia and sarcopenic obesity can increase the risk of CCVD and should be given adequate attention.

Despite the limited evidence available for the treatment of sarcopenia, significant efforts are being made to identify an effective therapy. Angiotensin-converting enzyme inhibitors appear to increase muscle blood flow to improve muscle contraction, strength, and function (*38*). However, meta-analyses have indicated that angiotensin-converting enzyme inhibitors (ACEIs) do not significantly improve walking distance or mitigate the age-related decline in muscle strength among older participants in clinical trials (*39*). The role of vitamin D supplementation in sarcopenia remains a topic of debate. An umbrella review of systematic reviews and meta-analyses (*40*) on pharmacological interventions for sarcopenia has examined ten different interventions, including vitamin D, combined estrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone-releasing hormone, combined testosterone-growth hormone, insulin-like growth factor-1, pioglitazone, testosterone, and ACEIs. Nevertheless, the most recent meta-analysis by Prokopidis *et al*. suggests that vitamin D supplementation does not improve sarcopenia indices and may even have detrimental effects on older adults (*41*). Future studies should focus on examining the impact of vitamin D supplementation on sarcopenia.

According to evidence-based medical research conducted by Yoshimura *et al*., exercise and physical activity, particularly resistance training, combined with nutritional supplementation have been identified as the most effective interventions for sarcopenia (*42*). This finding has been further supported by a recent network meta-analysis (*43*). Additionally, a recent meta-analysis of randomized controlled trials suggested that Tai Chi may also have beneficial effects for individuals with sarcopenia (*44*). However, aerobic exercise has not shown a positive effect on improving sarcopenia (*45*). Regarding dietary patterns, supplementation with branched-chain amino acids among older individuals has been associated with beneficial effects on muscle mass and strength (*46)*. However, the role of dairy protein in sarcopenia remains inconclusive (*47*). Therefore, it is essential to recognize the importance of gaining a better understanding of the underlying pathological mechanisms to facilitate the development of targeted treatments for sarcopenia.

4.3. Strengths and limitations of the study

The strength of this study lies in its extensive inclusion of a large number of patients, allowing for a robust assessment of the relationship between sarcopenia and incident CCVD. However, it is important to acknowledge the limitations of the methods employed in this study. These limitations are primarily attributable to the low quality and high heterogeneity of the individual participant data used in the meta-analysis. Although several potential confounders were identified, and sensitivity analyses were conducted, residual confounding remains a possibility. Additionally, the retrospective design of most of the included studies resulted in selection bias and limited the generalizability of the findings. Ultimately, we did not perform subtypes of CVD and cerebrovascular diseases as insufficient data were available.

5. Conclusion

In conclusion, our meta-analysis highlights the significant association between sarcopenia and sarcopenic obesity and the risk of developing CCVD. However, it is important to acknowledge the limitations inherent in the studies included in this review. To validate our findings and provide more robust evidence, prospective trials with large sample sizes are warranted. If future research strengthens the evidence, it may be prudent for current guidelines to consider incorporating early and regular cardio-cerebrovascular assessments for patients with sarcopenia.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

Author statement: Lei Guo conceived and designed the study. Miao Fang and Guo Tang carried out the literature search and screening of articles; Chunhua Liu and Chunling Li analyzed data. Miao Fang and Chunhua Liu wrote the manuscript. Lei Guo provided critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Review

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The status of surrogacy in China

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SUMMARY China's birth rates hit a record low in 2021. The high demand for having children has spawned a massive market for surrogacy, which, however, is a dilemma in China involving a series of moral and legal issues under the current circumstances. First, special populations, including infertile patients, families who have lost their sole child, and homosexuals, wanted to have children, giving rise to surrogacy. Then, the development of and innovation in assisted reproductive technology allowed surrogacy to mature. A high return offsets a high risk, and consequently, an underground surrogacy market has emerged, causing various social issues for the Chinese Government, such as civil disputes, gender disproportion, crime, and the spread of disease. At the same time, surrogacy violates moral ethics, traditional Chinese culture, and the rights and interests of vulnerable groups.

Keywords surrogacy, law, ethics, dilemma, social stability

1. Introduction

Surrogacy is an arrangement where a fertile woman bears and delivers a child to intended parents or persons, and surrogacy is classified into partial surrogacy (using an egg from the surrogate mother) and full surrogacy (without an egg from the surrogate mother) based on the source of the egg. Different surrogacy policies have arisen due to differing legislation, religious views, and social systems in each country (*1*). There are two types of surrogacies in countries with legal surrogacy: Commercial surrogacy aimed at direct financial gain and volunteer surrogacy (altruistic surrogacy) without direct financial gain but with remuneration (*2*). Surrogacy is not legal in China, but its legality has been heatedly discussed over the last few years (*3,4*). As new technological innovations have occurred in assisted reproductive technology (ART), the high demand for surrogacy has spawned a massive underground market in light of strict domestic restrictions on surrogacy. What will surrogacy lead to? This review explores the current status of surrogacy in China from the aspects of demand, traditional Chinese culture, ethics, legal rules, and social harm.

2. The reasons why surrogacy exists

2.1. Demand for surrogacy

In China, there are four main groups seeking surrogacy: Infertile patients, families who have lost their sole child, homosexuals, and others. In recent years, the prevalence of infertility among couples of childbearing age increased to 25% in China (*5,6*). This number is growing yearly for various reasons, including decreased sperm quality, female infertility, and other health problems (*7-9*). According to the data, only 32-41% of women achieve live birth with the help of ART, which cannot solve all of their issues (*10,11*). What is more, people who suffer from severe illnesses, such as heart failure, are unable to bear the burden of pregnancy. Therefore, surrogacy may become the sole solution for those people.

Families who have lost their only child and who cannot have another child tend to choose surrogacy services. Since the implementation of the family planning policy in 1982, Chinese couples were limited to a single child. As of 2018, China has more than 1,247,000 families whose only child is disabled or deceased (*12*). Older mothers have little chance of having another baby after losing a child (*13*). And yet the wish is never quenched, especially after the Chinese mainland's implementation of the two-child

policy in 2015 and the three-child policy in 2021. Influenced by the traditional Chinese concept of "bloodline inheritance," surrogacy is seen as a better choice than adoption. This can help them alleviate the mental grief caused by the loss of a child (*13,14*). Even some elderly people are influenced by the traditional Chinese belief in "more children, more blessings" and choose surrogacy in hopes of having more children, even though they no longer have the ability to raise them.

As homosexuals have been gradually accepted, raising children is assumed to stabilize same-sex relationships. With the advancement of ART and related industries such as sperm banking, *in vitro* fertilization (IVF), and surrogacy, homosexuals can now achieve their fertility goals (*15*). Moreover, a surrogacy incident involving a Chinese actress has brought surrogacy into the spotlight and exposed a certain segment of the female population who desire a child and do not want to face the risks of pregnancy or changes in body shape (*16*). Demand from all of these people have resulted in a surrogacy market in China.

2.2. Advances in ART

The advancement of life science technology has promoted a flourishing surrogacy market. The development of ART in particular has provided hope for people struggling with infertility, and the use of IVF has made surrogacy a reality (Figure 1). Before ART, conventional surrogacy would help wives who could not become pregnant. In 1978, the world's first test-tube baby was born at Cambridge University in England through the joint efforts of Professor Edwards and Dr. Steptoe, enabling a gestational surrogate to carry a child genetically unrelated to the surrogate mother but the intended parent. Then, the first successful gestational surrogacy took place in 1985 (*17*). ART procedures involve IVF, intracytoplasmic sperm injection (ICSI), cryopreservation of gametes or embryos, and fertility medication. For those with low sperm counts or poor-quality sperm, high-quality sperm can be combined with eggs through ICSI. Moreover, preimplantation genetic testing is often used to deal with a possible genetic disorder; preimplantation genetic diagnosis technology can help to select the sex and characteristics of surrogate children (*18,19*). The latter method may make surrogacy popular. In addition, reproductive freezing technology allows people to store gametes for long periods to have their children at any age and stage of life. For instance, human sperm banks provide cryopreservation of spermatozoa services for males needing to preserve fertility for an extended period. As of now, there are 27 Chinese regional sperm banks affiliated with the sperm banking network on the Chinese mainland (*20*).

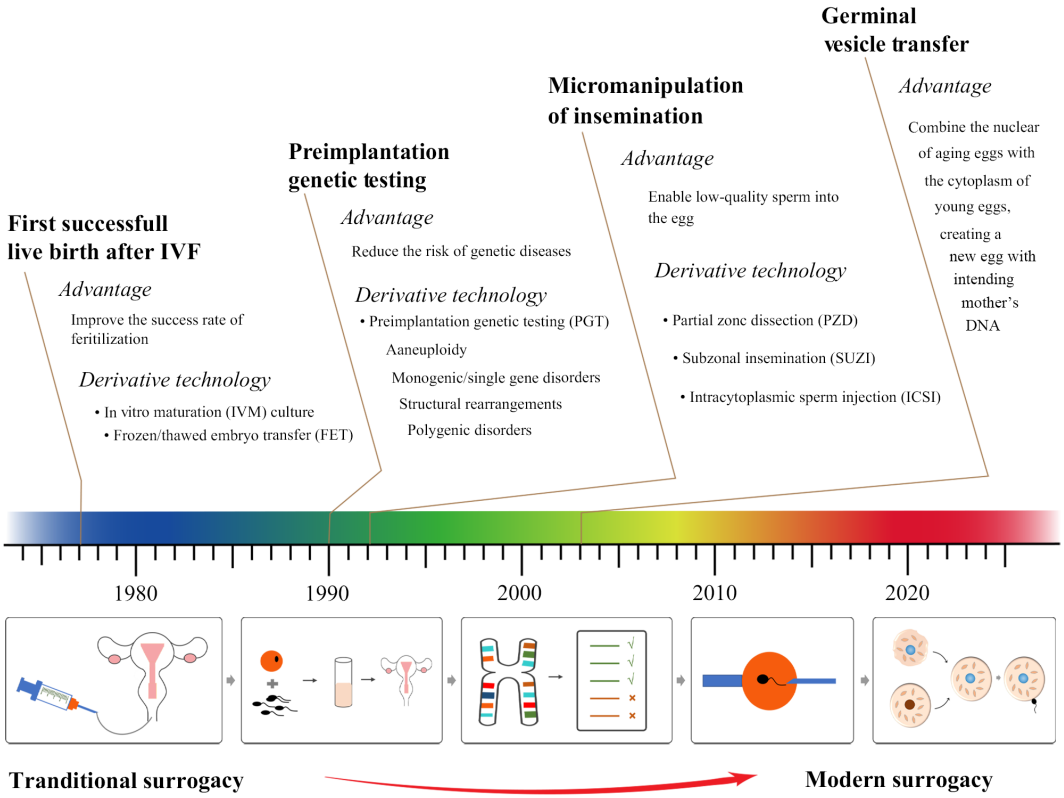

Figure 1. The maturation of surrogacy along with the development of IVF. IVF: *in vitro* fertilization.

2.3. The impetus of practical interests during surrogacy

The surrogacy industry is booming globally and is expected to grow at a compound annual growth rate of 24.5% from 2023 to 2032. In 2018, surrogacy was a $6 billion business with an annual growth of 24.5%. The global surrogacy market was valued at over USD 14 billion in 2022 (*21*). In some countries like Mexico, surrogacy as an emerging economy is supposed to promote economic growth. Surrogacy has become a bottomless market, along with the flourishing of private surrogacy firms. The surrogacy agency is the central link responsible for coordinating multiple parties, including couples wanting to have children, egg donors, surrogate mothers, surrogate doctors, and hospitals that issue birth certificates. Chinese families tend to choose cross-border surrogacy in countries where commercial surrogacy is legal and has a complete industrial chain. The surrogacy fees are expensive for ordinary families, with legal surrogacy costs ranging from $80,000 to $120,000 in the US (*22*). About one-third of the profits are reaped by intermediaries; the rest is for clinics, drugs, surrogates, and attorney fees. The cost is relatively cheap in some economically underdeveloped regions, such as Ukraine, where prices are about one-fifth of those in the US. According to reports, Ukraine has about 2,000-4,000 children born through surrogacy every year, one-third of whom come from Chinese clients (*23*). Due to COVID-19 and the armed conflict in Ukraine, domestic surrogacy rapidly surpassed cross-border surrogacy in the surrogacy market after 2020 in China (*23,24*).

2.4. Rising awareness of human rights

With the economic development and improvement of women's status, respect and protection for females have been highlighted more than ever before. Some liberals uphold the view that women should be allowed to use their bodies and be paid as they wish and that voluntary surrogacy is an expression of bodily integrity, just like abortion rights (*25-27*). A poll in the Chinese city of Guangzhou found that people would accept the profession of surrogate mothers and it proposed greater compensation than the current market price for surrogacy (*28*).

A well-known fact is that most surrogate mothers from humble origins are motivated by payment; hence, surrogacy has been criticized for exploiting and commercializing women and children. Commercial surrogacy prices surrogate mothers based on their appearance, education, and health (*29*), commercializing women as a "surrogate uterus" (*30*). This commodification contradicts Kant's moral dictum to "Act to treat humanity, whether yourself or another, as an end-in-itself and never as a means" (*31*). Moreover, surrogacy forcibly removes the natural emotions between a surrogate mother and her child, which is an inhuman act (*32*). Surrogacy also makes a "child" (or fertilized eggs) a business (*33*). It permits infants to be born based on the expectations of the intended parents, and especially the choice of genetics and sex, while children with physical flaws would be abandoned as "defective products" (*29,34*). That said, considering the right to control one's body and birthright, surrogacy seems to allow the intended parents to exercise their reproductive rights (*35,36*).

3. The drawbacks of the current chaotic surrogacy market

3.1. Surrogacy runs counter to moral ethics and traditional Chinese culture

Surrogacy challenges the values of family, traditionally defined as marriage, sex, and fertility. Surrogacy has broken those three elements apart and impacted the conventional views, including the ancient inheritance system that has been followed for thousands of years on the Chinese mainland (*35*). Chinese people consider ancestral inheritance to be the continuation of ancestral blood and genes, so "there are three kinds of unfilial behavior, and no offspring is the most serious" is a humanistic concept deeply rooted in their minds. Asset inheritance follows the same primogeniture rules as family inheritance (*37*). A child born through surrogacy is often turned away from inheriting the traits of their ancestors. Surrogate families and children are often discriminated against because surrogacy is condemned for undermining social customs and the family structure and violating dignity (*38*). In some countries, an immediate family member usually serves as the surrogate mother, such as a 51-year-old mother in the US who birthed a healthy girl through surrogacy for her daughter (*39*). Surrogacy poses problems for family ethics, as the Chinese have always placed a high value on relatives. Moreover, renting a uterus is regarded as a selfish, unfilial, and irresponsible act that draws strong condemnation in the traditional Chinese belief that "skin and hair are inherited from your parents." Therefore, surrogacy is an affront to human morality and traditional Chinese culture.

3.2. Surrogacy violates the rights and interests of vulnerable groups

3.2.1. Surrogate mothers

The lack of applicable laws often infringes surrogate mothers' lawful rights and interests. Since the employment relationship between surrogate mothers and surrogacy agencies or commissioning parents is not recognized by Chinese law, surrogate mothers' lawful rights and interests, including the right to

informed consent, personal freedom, and reasonable compensation, are often beyond the reach of legal protection. Underground surrogacy agencies conceal the truth from surrogate mothers during medical examinations. A surrogate mother can have several embryos implanted, have partial embryonic development terminated, or have labor induced without her permission (*40*). Several underground surrogacy agencies even restrict surrogate mothers' freedom and force them to work (*29*). On the Chinese mainland, surrogate mothers tend to be low-income women who need money (*41*). If the surrogate mother does not give birth to a healthy child as expected, all of her efforts will be in vain, and she will even have to return the relevant fees. Moreover, due to the prohibitive attitude of Chinese law, surrogate mothers have difficulty obtaining legal help regarding their rights or interests. Once intended parents breach the contract, the surrogate mother has to raise the child alone, which would undoubtedly increase the burden on her.

In addition, IVF complications should be taken into consideration, such as multiple pregnancy and ovarian hyperstimulation syndrome, a life-threatening iatrogenic issue (*11*). IVF-related medical malpractice may cause substantial emotional, physical, and financial expenses in fertility care (*42*). Since traditional Chinese social concepts are unsupportive of surrogacy, surrogate mothers' spiritual and material safety are often under pressure from public opinion. In short, surrogacy violates the surrogate mother's rights and interests.

3.2.2. Children born from surrogacy

The most prominent and controversial topic about surrogate children on the Chinese mainland is the inability to identify their parentage. Their custody, support, inheritance, and parental support obligations are legally unprotected (*43*). Although the laws of the Chinese mainland are not in favor of surrogacy, the existence of surrogate children is undeniable, and surrogate children should not pay for the mistakes made by their parents and imperfect laws. In Hong Kong, intended parents can obtain parental rights through parental orders in favor of gamete donors, but there is no similar provision on the mainland (*44*). Based on previous cases involving guardianship disputes, the legal mother is determined by the principle that "the one who gives birth is the mother" and the legal father is defined by "genetics." This situation increases the likelihood of surrogate children being born without a legal guardian. Regardless of who the legal parents are, the bifurcated identity of the "mother" can cause grievous emotional distress to the child (*45*). The problem becomes more complicated with transnational surrogacy. Due to the discrepancies in surrogacy attitudes and legal regulations in different countries, the surrogate child may not be legally recognized in other countries. India and a few states in the US support surrogacy, stipulating that the legal parents of a surrogate child are the intended parents. At the same time, the fact that law on the Chinese mainland does not recognize surrogate children could prevent the child from obtaining citizenship in the country of birth or adoption (*46,47*).

In addition, whether surrogate children should have the right to know the truth and whether privacy should be protected is controversial. If the surrogate children are not informed that their genes are not inherited from the parents who raised them, this potentially increases the risk of "inbreeding" (*48,49*). However, the disclosure of surrogacy will undoubtedly have a great impact on surrogate children's physical and mental health in the current social context (*48,50*). More importantly, the law on the Chinese mainland rarely involves the lawful rights of surrogate children. Usually, judges protect the interests of the surrogate child as much as possible in accordance with the "best interests of the child" principle established by the United Nations. Nevertheless, the children are incapable of suing independently or hiring an attorney who can make reasonable recommendations to a judge. When their interests are violated, they cannot seek legal protection.

3.2.3. Families who choose surrogacy

As a result of the high demand for surrogacy, legal prohibition will force surrogacy into the shadows, and surrogacy agencies will raise the price of surrogacy when demand exceeds supply. The interests of surrogate families are likewise at risk due to the lack of legal protection. According to existing cases involving surrogate parental rights disputes in China (*51*), the principle of "the one who gives birth is the mother" often results in the intended parents' loss of money and the child. Some illegal actors even take advantage of intended parents' desire for a child to scam them. Due to the generally unsupportive attitude towards surrogacy, successful surrogate families usually bear a tremendous emotional burden. They tend to conceal the fact of surrogacy to avoid criticism based on traditional concepts.

3.3. Surrogacy induces social harms

Surrogacy may contribute to social problems such as civil disputes, gender disproportion, crime, and the spread of disease, resulting in social instability. First, surrogacy can lead to civil disputes and social disharmony. *i*) The number of lawsuits over child parentage and remuneration increases, and *ii*) Class issues became more acute, and wealthy people use money to hire poor people to bear their children (*52,53*). Second, since some surrogacy agencies offer parents the option of choosing a baby's sex, Chinese parents would be inclined to select boys in the traditional belief of

"valuing men over women," leading to an imbalance in the gender proportion in the long run and exacerbating conflicts of gender bias. Third, surrogacy would spur crimes such as prostitution, trafficking, and entrapment of women and children (*48,54-56*). Unscrupulous groups may rely on "scarce technology" to reap exorbitant profits. Women in poor areas, and especially female students and minors, can easily be exploited, oppressed, and cheated by an unregulated underground surrogacy market (*29,57*). Fourth, the unregulated underground surrogacy market lacks industry standards and technical regulations, resulting in a harsh medical environment and conditions, physical defects, and infectious diseases (*24,58*). Surrogate children who have congenital illnesses may be abandoned after birth (*56*). A rampant underground market in surrogacy will negatively affect the government's oversight of the medical sector (*59*). All of the aforementioned issues are detrimental to family and social harmony (*60*).

4. The current legal system of surrogacy in China

Surrogacy usually involves IVF, in which the provider's egg and sperm are combined outside the body and then implanted into a surrogate mother's uterus to complete the pregnancy and delivery. Although the Chinese Government does not prohibit surrogacy in law, some clauses indirectly restrict access to eggs, embryos, and related technologies (Figure 2). According to the National Health Commission's 2001 approach to managing human ART, the sale of gametes, zygotes, and embryos was prohibited in any form (*61*). In 2003, the Ministry of Health issued measures to manage ART, which prohibited commercial embryo donation and

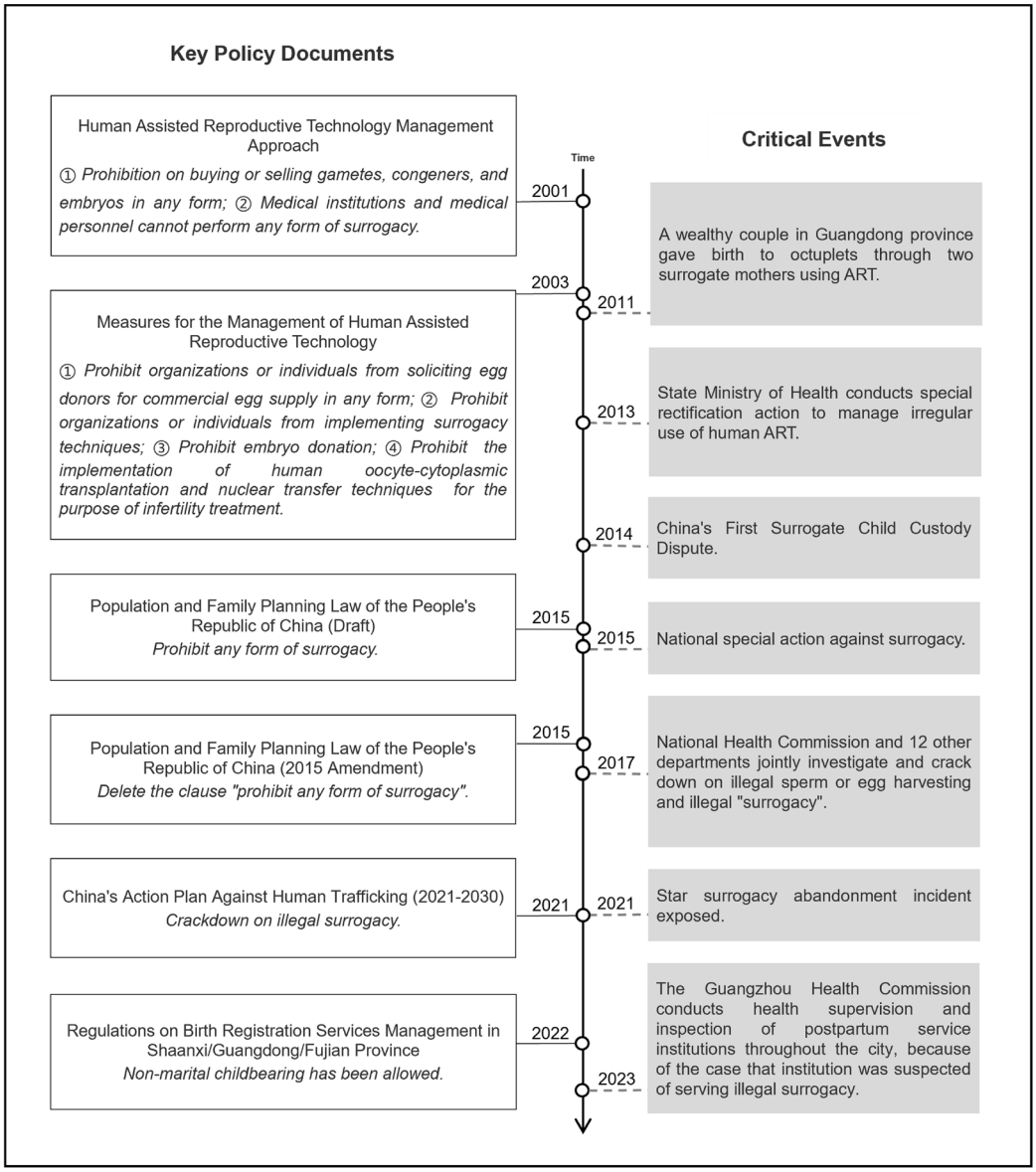

Figure 2. Brief timeline of key policy documents and critical events related to surrogacy on the Chinese mainland. Key policy documents are main policies related to surrogacy. Typical social cases and special state actions against surrogacy are cited as critical events.

surrogacy performed by medical facilities (*62*). Subject to these two laws, surrogacy cannot be performed by medical facilities or personnel, but the law does not cover ordinary citizens. Therefore, there is no unified or overall value judgment on the issue of surrogacy on the Chinese mainland. In contrast, the law of surrogacy in the Hong Kong Special Administrative Region is clear, allowing altruistic surrogacy and prohibiting commercial surrogacy; the Human Reproductive Technology Ordinance requires that the intended parents should be heterosexual couples and use their own sperm or eggs for surrogacy (*63*). In reality, intended parents inevitably pay the surrogate mother, and those couples with declining gamete quality have to use the gametes of others, which is illegal in Hong Kong.

Surrogacy is generally considered a violation of "public order and good customs" on the Chinese mainland. Due to the negative attitude toward surrogacy under the law on the mainland, the surrogacy agreements signed between intended parents and surrogate mothers often lead to awkward situations in court rulings. The surrogacy contract is deemed invalid, evidenced by the conclusions of most civil disputes in line with the Civil Code of the People's Republic of China (*64*). This has sparked a debate over surrogacy contracts. Most scholars believe that the judge's ruling on "public order and good customs" is unjust based on the judge's personal views (*56*). In Hong Kong, a surrogacy agreement is permitted and must be signed voluntarily, which can protect both parties' lawful rights and interests (*63,65,66*).

The Chinese Government has conducted several special campaigns against surrogacy over the past decade, but there has been little discernible improvement (*67*). Two factors may explain this. On the one hand, the Chinese mainland lacks universal legal restrictions and long-term administrative supervision over the complex market environment, and especially transnational surrogacy (*56,68*). That said, compared to the illegal benefits of surrogacy, the punishment imposed by the special campaigns is negligible, contributing to the lack of legal oversight on surrogacy agencies (*29*). The underground surrogacy market has gradually grown despite repeated prohibitions. In general, China explicitly prohibits surrogacy, but this ban can no longer be fully enforced for various reasons.

5. Conclusion

The demand for surrogacy is growing and coincides with the population's desire for children. This has led to the emergence of a Chinese underground market, which has flourished along with the development of ART. However, surrogacy involves many social issues, such as countering traditional Chinese concepts, infringing on the lawful rights of vulnerable groups, and impacting social harmony, so China's approach to surrogacy is still a long way from being finalized.

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Impact of sarcopenia on S1 adjuvant chemotherapy and prognosis in pancreatic cancer patients

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SUMMARY Although the importance of adjuvant chemotherapy (AC) has been recognized in pancreatic cancer (PC) patients, there are few studies to address the underlying mechanisms of failure to complete AC. This study aims to investigate the relationship between nutritional state represented by sarcopenia and failure to complete AC in patients after curative-intent surgery for PC. This study included 110 patients who underwent pancreaticoduodenectomy for potentially resectable pancreatic cancers with intention of adjuvant S-1. Sarcopenia was defined using the psoas muscle mass index with cutoff values of 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women, which were calculated with a 3-D volumetric software. The relation between sarcopenia and successful AC and long-term survival were investigated. Twenty-nine (26%) patients were diagnosed as having sarcopenia (Sarcopenia group). Sarcopenia group comprised significantly older patients than Non-sarcopenia group (72 *vs*. 67 years old, $p = 0.0087$). AC was successfully completed in 14 patients (48%) in Sarcopenia group compared to 72 patients (89%) in Non-sarcopenia group ($p < 0.0001$). Multivariate analysis identified age ≥ 70 years and sarcopenia as significant risk factors for failure of AC. Among patients ≥ 70 years old, rate of successful AC was significantly higher in sarcopenia groups than non-sarcopenia group (17% *vs*. 78%, $p < 0.001$). In conclusions, age and sarcopenia were critical risk factors for the failure of 6 months of adjuvant chemotherapy. Among elderly patients, sarcopenia can predict the poor success rate of AC.

Keywords pancreatic cancer, sarcopenia, adjuvant therapy, nutrition, prognosis

1. Introduction

Despite recent improvements in diagnostic and therapeutic modalities, pancreatic cancer (PC) still has an extremely poor prognosis (*1*). Although only surgery may lead to a complete cure, most patients develop recurrence even after curative-intent surgery (*2,3*) . At present, adjuvant chemotherapy (AC) is one of the mainstays for the treatment of resectable PC (*4-6*) . A recent large-scale clinical study has shown that the completion of planned AC rather than early initiation was a critical prognostic factor for patients with PC (*7*) . For PC patients, pancreaticoduodenectomy has been established as a standard procedure. Although the importance of the completion of AC has been recognized, there are few studies to address the underlying mechanisms of failure to complete AC in PC patients.

In 2013, the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01) phase III trial demonstrated that S-1 was significantly more effective than gemcitabine as an AC for Japanese patients who underwent curative surgery for PC (*5*) . Therefore, AC with S-1 after curative surgery is considered the standard therapy for these patients in Japan.

We hypothesized that nutritional factors would have a significant relation to the capacity of each patient to complete the planned adjuvant therapy after pancreaticoduodenectomy for PC patients. Here we investigated the clinicopathological, sarcopenia, and nutrition state factors associated with failure to complete AC in patients after curative-intent surgery for PC.

2. Patients and Methods

2.1. Patients

This single-center retrospective study was approved by the institutional review board of the Cancer Institute

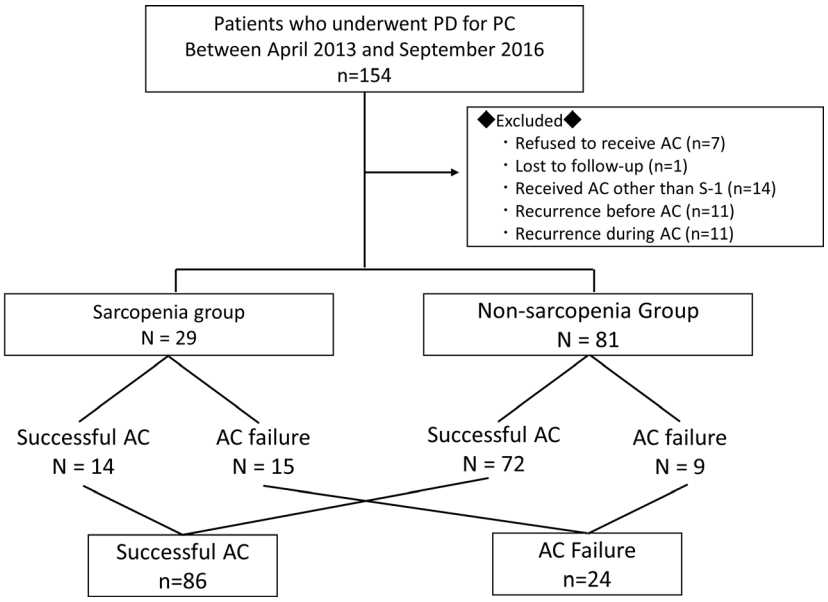

Figure 1. Patient flow of this study.

Hospital with waived informed consent (ID number: 2017-GA-1019-0040). From April 2012 to March 2015, 154 patients with potentially resectable PC underwent pancreaticoduodenectomy with curative intent at Cancer Institute Hospital, Tokyo, Japan. We excluded; (1) 14 patients who received AC other than S-1; (2) 7 patients who refused to receive AC; (3) 11 patients who had early recurrence before AC introduction; (4) 11 patients who had recurrence during AC; (5) 1 patient who we lost to follow-up (1 patients). Finally, 110 patients were the subject of analysis in the present study. A flow diagram of the patient selection is shown in Figure 1.

2.2. Perioperative nutritional management

All patients underwent pancreaticoduodenectomy with regional lymph nodes (LNs) nodal dissection with or without nerve plexus dissection. In principle, hemi-circumferential dissection of nerve plexus around the superior mesenteric artery (SMA) was conducted in patients with suspicious or apparent perineural invasion toward the SMA (*8,9*). After admission, patients were treated in accordance with our clinical pass for pancreaticoduodenectomy. In brief, patients ate ordinal meals until night two days before the surgery, took liquid nutrition on the day before surgery, and drank one liter of oral rehydration solution until 3 h before surgery. After surgery, the nasogastric tube was removed just after airway extubation. Oral intake was initiated on postoperative day (POD) 1, beginning with pure water. Patients began to eat liquid food on POD 4, starting with rice gruel and soft food on POD 6 and advancing in steps to regular food intake. If the patient had a finding of clinically relevant postoperative pancreatic fistula, conservative treatment with prolonged drain placement was chosen (*10,11*) . Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) were defined based on international guidelines (*12,13*) . Other postoperative complications were defined according to the Clavien-Dindo classification (*14*) .

2.3. Adjuvant Chemotherapy

AC was administered after confirming sufficient patient recovery for chemotherapy based on oral intake, performance status, and absence of intractable diarrhea. The patients received S-1 chemotherapy and were followed on an outpatient basis. The patients received 40 mg of S-1 per square meter of body surface area twice a day for 4 weeks, followed by 2 weeks of rest as one course (6-week schedule), and this was continued for 6 months after surgery. The patients with a body surface area < 1.25 m^2 received 80 mg daily, those with a body surface area of 1.25 m^2 or more, but < 1.5 m^2, received 100 mg daily, and those with a body surface area of 1.5 m^2 or more received 120 mg daily.

The need for a reduction of the starting dose, a delay in treatment, or a dose reduction in the patients who received S-1 in clinical practice was determined following the criteria of the JASPAC-01 trial (*5*) . Briefly, the treatment was delayed when patients had hematological adverse events of grade 3 or more, or non-hematologic adverse events of grade 2 or more, until all adverse events recovered to grade 0 or 1, and then was started at a reduced dose of 100, 80 or 50 mg, based on the body surface area described above. The patients who started with the 6-week schedule of S-1 and experienced the adverse events described above at a reduced dose were switched from the 6-week schedule to a 3-week schedule (2 weeks of treatment followed by 1 week of rest).

2.4. Follow-up during S-1 treatment

In principle, patients underwent hematologic tests and assessments of clinical symptoms every 2 weeks during adjuvant therapy. The presence of relapse was determined using imaging studies, including ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), appropriately. Patients underwent at least one of these imaging examinations at 3-month intervals during S-1 treatment. We defined achievement of more than 6 months of S1 adjuvant therapy as "successful adjuvant therapy" based on a previous report (*9*) .

2.5. Evaluation of clinical parameters and sarcopenia

The toxicities during adjuvant chemotherapy were graded according to the CTCAE ver. 4.0 criteria. Renal impairment was measured in terms of the creatinine clearance (CCr), calculated by the formula proposed by Cockroft and Gault (*15*). For the evaluation of the volume of skeletal muscle, we measured the psoas muscle mass index (PMI, cm^2/m^2) (*16*). Cross-sectional areas of the left and right psoas muscles at the level of the third lumbar vertebra (L3) were estimated in our study population. This was accomplished by first identifying individual vertebral levels on each patient's CT scan. We then selected the individual imaging slice at the superior aspect of L3 and outlined the borders of the left and right psoas muscles. The area of the resulting enclosed regions was then computed to generate the cross-sectional area of the psoas muscles. These steps were completed in a semi-automated fashion using algorithms programmed in VINCENT. We defined sarcopenia using sex-specific cutoff values of PMI, which were 6.36 cm2/m^2 for men and 3.92 cm^2/m^2 for women according to the previous report (*16*). As a barometer of nutritional assessment, Onodera's prognostic nutritional index (PNI) was used. The preoperative PNI was calculated as 10 × albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3) (*17*).

2.6. Statistical analyses

Patients were categorized into two groups regarding the presence of sarcopenia on preoperative CT findings (sarcopenia group, 29 patients; non-sarcopenia group, 81 patients). The clinicopathological parameters between groups were compared using the Mann-Whitney *U* test and the Fisher's exact test as appropriate. Continuous variables were expressed as median values with range. A multiple logistic regression analysis was used to identify the factors independently associated with failure to more than 6 months of AC.

Statistical analyses were performed using JMP statistical discovery software (JMP version 11.0; SAS Institute, Cary, NC). p value less than 0.05 was considered statistically significant.

3. Results

3.1. Background and short-term outcomes

Table 1 shows the patient's demographics and surgical outcomes. Sixty-three patients (57%) were male. Sixteen patients (15%) received neoadjuvant chemotherapy. Twenty-nine patients (26%) needed preoperative drainage of the biliary tract. The median value of PMI was 7.11 cm^2/m^2 in male patients and 4.71 cm^2/m^2 in female patients. Twenty-nine (26%) patients were diagnosed as having sarcopenia (Sarcopenia group). Sarcopenia group comprised significantly older patients than Non-sarcopenia group (72 *vs*. 67 years old, p = 0.0087). Preoperative CEA, CA19-9, and tumor size were not significantly different between groups (CEA, 3.2 *vs*. 2.4 ng/mL, p = 0.08: CA19-9, 68.4 *vs* 86.7 IU/L, p = 0.78; size, 3.4 *vs*. 3.0 cm, p = 0.76). Operation duration, estimated intraoperative blood loss, and incidence of blood transfusion were similar among groups. Hemi-circumferential dissection of nerve plexus around the SMA was likely performed more frequently in non-sarcopenia group than sarcopenia group, but not statistically significant (68% *vs*. 52%, p = 0.13). Postoperative pancreatic fistula, delayed gastric emptying, surgical site infections, and diarrhea were similarly observed among groups. Complications equal to or greater than Clavien-Dindo grade IIIa were more frequent in sarcopenia groups than non-sarcopenia group (17% *vs*. 2%, p = 0.0133). Postoperative hospital stay and mortality rate were not significantly different among groups. R0 resection rate (100% *vs*. 96%, p = 0.2933) and incidence of pathological positive lymph node (72% *vs*. 73%, P = 0.29) were similar among the groups.

3.2. Adjuvant Chemotherapy

Table 2 shows the details of AC in the whole cohort including reasons for failure of AC in 24 patients of the failure group. AC was completed in 14 patients (48%) in Sarcopenia group compared to 72 patients (89%) in Non-sarcopenia group ($p < 0.0001$). Among 24 patients with unsuccessful AC, it was abandoned in 10 patients mainly due to poor performance status or insufficient oral intake. The reasons for discontinuation in 14 patients included fatigue in 4 patients, anorexia in 2 patients and other symptoms.

Univariate analysis revealed that age ≥ 70 years ($p < 0.0001$), sarcopenia ($p < 0.0001$), serum CEA ≥ 2.7 ng/dL (p = 0.0103), tumor size ≥ 3.2 cm (p = 0.0146) and CCr < 60 mL/min (p = 0.0004) were significant risk factors for failure to achieve 6 months of AC. Multivariate analysis identified age ≥ 70 years (odds ratio [OR], 21.9; 95% confidence interval [CI], 4.01 to 120.29; p = 0.0004) and sarcopenia (OR, 6.98; 95% CI, 1.83 to 26.50; p = 0.0044) as significant risk factors for failure of successful AC (Table 3).

Table 1. Patients characteristics, surgical outcomes, and postoperative complications

Variables	Total $n = 110$	Sarcopenia $n = 29$	Non-sarcopenia $n = 81$	p-value
Age, years	68 (46-86)	72 (54-86)	67 (46-80)	0.009
Male: Female	63: 47	18: 11	45: 36	0.66
Body mass index, kg/m^2	21.5 (15.8-28.3)	20.0 (15.8-26.6)	22.0 (17.1-28.3)	0.0008
Prognostic nutritional index	40.5 (22.0-51.0)	40.0 (29.0-45.0)	41.0 (22.0-51.0)	0.35
Diabetes, *n* (%)	43 (39%)	15 (52%)	28 (34%)	0.13
Neoadjuvant chemotherapy, *n* (%)	16 (15%)	6 (20%)	10 (12%)	0.36
Preoperative drainage of bile duct, *n* (%)	39 (36%)	11 (38%)	28 (35%)	0.14
CEA, ng/mL	2.7 (0.5-19.8)	3.2 (0.9-19.8)	2.4 (0.5-16.7)	0.076
CA19-9, IU/L	80.6 (2-50,000)	68.4 (2-2,859.5)	86.7 (2-50,000)	0.78
UICC stage (IA/IB/IIA/IIB/III)	8/18/4/46/33	3/5/0/10/11	5/13/4/36/22	0.51
Tumor size, cm	3.2 (0.5-9.6)	3.4 (0.5-7.1)	3.0 (1.4-9.6)	0.76
Operative time (min)	501 (363-920)	517 (384-920)	500 (363-777)	0.62
Estimated blood loss (mL)	540 (85-2,700)	540 (180-1,830)	540 (85-2,700)	0.98
Intraoperative blood transfusion, *n* (%)	0 (0-1,360)	5 (17%)	6 (7%)	0.15
Nerve plexus dissection of the SMA	70 (64%)	15 (52%)	55 (68%)	0.22
R0 resection rate (0/1)	107/3	29/0	78/3	0.29
incidence of pathologically positive lymph node	80 (72%)	21 (72%)	59 (72%)	0.96
Pancreatic fistula ≥ grade B, *n* (%)	20 (18%)	4 (14%)	16 (20%)	0.58
Delayed gastric emptying ≥ grade B, *n* (%)	16 (14%)	5 (17%)	11 (14%)	0.76
Organ/space SSI, *n* (%)	34 (30%)	9 (32%)	25 (31%)	1.00
Diarrhea, *n* (%)	37 (33%)	10 (34%)	27 (33%)	0.98
Clavien-Dindo Classification ≥ IIIa, *n* (%)	7 (6%)	5 (17%)	2 (2%)	0.013
Pleural effusion	1	0	1	
Ascites	2	2	0	
Intraabdominal bleeding	2	1	1	
Sepsis	1	1	0	
Postoperative hospital stay (days)	26 (12-106)	28 (16-106)	25 (12-63)	0.20
Mortality	1 (1%)	1 (3%)	0 (0%)	0.26

Continuous data are expressed as median with range. SSI, surgical site infection; SMA, Superior mesenteric artery.

Table 2. The details of failure of adjuvant therapy

Type		Grade 1/2/3/4/5
Abandoned	10	
Poor performance status	4	-
Insufficient oral intake	4	-
Neutropenia	1	-
Postoperative complication	1	-
Withdrawn after initiation of chemotherapy	14	
Fatigue	4	0/4/0/0/0
Anorexia	2	0/2/0/0/0
Pigmentation	1	0/1/0/0/0
Arrhythmia	1	1/0/0/0/0
Hyperglycemia	1	0/0/1/0/0
Eye tearing	1	1/0/0/0/0
Neutropenia	1	0/1/0/0/0
Dehydration	1	0/0/1/0/0
Liver dysfunction	1	1/0/0/0/0
Sepsis	1	-

When we examined patients who were 70 years or over, rate of successful AC was significantly lower in sarcopenia groups than non-sarcopenia group (3 patients (17%) *vs*. 23 patients (78%), $p < 0.0001$, Table 4).

3.3. Long-term Survival

Overall survival was compared between 29 sarcopenia patients and 81 non-sarcopenia patients, with a follow-up period of at least 15 months. In comparison with sarcopenia, a significantly higher OS was observed in non-sarcopenia (Figure 2A, $p = 0.017$, Median survival time (MST); 44 *vs*. 25 months). Overall survival was compared between the patients with failed AC and those with successful AC. Thirteen of 24 patients with failed AC, and 26 of 86 patients with successful AC, with a follow-up period of at least 15 months. A significantly higher OS was observed in the patients with successful AC than those with failed AC (Figure 2B, $p = 0.001$. MST; 44 *vs*. 24 months).

4. Discussion

In this study, we investigated the profile of AC after pancreaticoduodenectomy for PC and analyzed the relationship between AC failure and preoperative sarcopenia, which was defined based on cross-sectional areas of the left and right psoas muscles at the third lumbar spine. Our results indicated that sarcopenia was the significant risk factor for failure to complete the planned AC. To the best of our knowledge, this is the first report to reveal the strong correlation between sarcopenia and AC in patients with PC. In this series, we used sarcopenia using sex-specific cutoff values for PMI were 6.26 cm^2/m^2 for men and 4.64 cm^2/m^2 for women, and we used the sarcopenia using sex-specific cutoff values for PMI were 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women according to the previous report. But

Table 3. Univariate and Multivariate analysis or risk factors associated with failure to more than 6 months of planned adjuvant chemotherapy

Variables		Univariate analysis		Multivariate analysis	
	n	Odds ratio (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value
Age (years)		25.38 (5.55-115.9)	< 0.0001	21.97 (4.01-120.29)	0.0004
≥ 70	48				
< 70	62				
Gender		1.45 (0.58-3.61)	0.42		
Female	47				
Male	63				
Diabetes		1.42 (0.57-3.56)	0.45		
Present	43				
Absent	67				
Neoadjuvant chemotherapy		0.80 (0.20-3.08)	0.75		
Present	16				
Absent	94				
CEA (ng/ml)		3.79 (1.37-10.47)	0.01	1.89 (0.49-7.23)	0.35
≥ 2.7	56				
< 2.7	54				
CA19-9 (U/ml)		2.41 (0.93-6.22)	0.07		
≥ 80.6	55				
< 80.6	55				
Body mass index (kg/m^2)		1.02 (0.41-2.54)	0.95		
< 22	59				
≥ 22	51				
Sarcopenia		8.57 (3.13-23.42)	< 0.0001	6.98 (1.83-26.50)	0.004
Present	29				
Absent	81				
Creatinine clearance		6.43 (2.27-18.17)	0.0004	1.93 (0.48-7.77)	0.35
< 60	21				
≥ 60	89				
Prognostic nutritional index		1.60 (0.64-3.99)	0.31		
< 37	45				
≥ 37	65				
UICC stage		0.87 (0.34-2.18)	0.77		
≥ II B	67				
< II B	43				
Size (cm)		3.78 (1.37-10.47)	0.01	3.64 (0.94-14.07)	0.06
≥ 3.2	56				
< 3.2	54				
Estimated blood loss (ml)		0.60 (0.24-1.51)	0.28		
≥ 540	56				
< 540	54				
Operation duration (min)		0.47 (0.18-1.20)	0.12		
≥ 500	57				
< 500	53				
Intraoperative blood transfusion		3.50 (0.96-12.72)	0.06		
Present	11				
Absent	99				
Pancreatic fistula		0.57 (0.15-2.17)	0.42		
≥ grade B	20				
< grade B	90				
Delayed gastric emptying		1.23 (0.35-4.23)	0.74		
≥ grade B	16				
< grade B	94				
Organ/space SSI		1.46 (0.56-3.77)	0.43		
Present	34				
Absent	76				
Diarrhea		0.76 (0.28-2.05)	0.60		
Present	37				
Absent	73				

CI, confidence interval; UICC, Union for International Cancer Control; SSI, surgical site infection.

there were comparable results.

In the current series, sarcopenia was a predictor of survival following pancreaticoduodenectomy as well, with sarcopenic patients having a significantly increased risk of death. Sarcopenia has been reported to be an objective measure of patient frailty that was strongly associated with long-term outcomes independent of tumor-specific factors. Peng *et al*. have recently reported that total psoas area (TPA) was measured on preoperative cross-sectional imaging in 557 patients undergoing resection of pancreatic adenocarcinoma between 1996 and 2010 (*18*). Sarcopenia was defined as the presence of a TPA in the lowest sex-specific quartile. The impact of sarcopenia on 90-day, 1-year, and 3-year mortality was assessed relative to other clinicopathological factors. Sarcopenia was associated

Table 4. Surgical outcomes and postoperative complications among elderly patients

Variables	Sarcopenia, *n* = 18	Non-sarcopenia, *n* = 30	*p*-value
UICC stage (IA/IB/IIA/IIB)	0/1/8/9	0/2/9/19	0.60
Tumor size, cm	3.6 (1.8-7.1)	3.0 (1.4-4.5)	0.14
Estimated blood loss, mL	505 (205-1,830)	540 (150-2,700)	1.0
Operative time, min	479 (384-920)	490 (363-777)	0.73
Intraoperative blood transfusion, mL	0 (0-1360)	0 (0-560)	0.27
Nerve plexus dissection of the SMA	8 (44%)	22 (73%)	0.02
Pancreatic fistula ≥ grade B, *n* (%)	3 (17%)	5 (17%)	1.0
Delayed gastric emptying ≥ grade B, *n* (%)	4 (22%)	4 (13%)	0.75
Diarrhea, *n* (%)	5 (28%)	15 (50%)	0.20
Clavien-Dindo Classification ≥ III, *n* (%)	4 (22%)	3 (10%)	0.25
Postoperative hospital stay (days)	33 (16-106)	28 (16-63)	0.32
Mortality, *n* (%)	1 (5%)	0 (0%)	0.19
Successful adjuvant chemotherapy, *n* (%)	3 (17%)	23 (78%)	< 0.0001

Continuous data are expressed as median with range. SSI, surgical site infection; SMA, Superior mesenteric artery

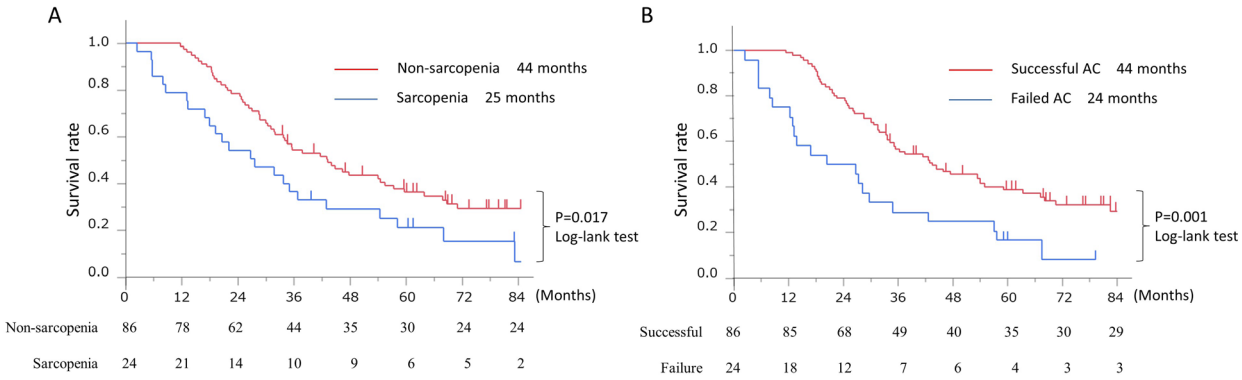

Figure 2. Kaplan-Meier analysis of overall survival according to sarcopenia or successful adjuvant chemotherapy. A: Significantly higher overall survival was observed in patients with non-sarcopenia than those with sarcopenia (p = 0.017, Median survival time (MST); 44 *vs*. 25 months). **B:** Significantly higher overall survival was observed in patients with successful adjuvant chemotherapy than those with failure of adjuvant chemotherapy (p = 0.017, MST; 44 *vs*. 24 months).

with an increased risk of 3-year mortality (HR = 1.68; $p < 0.001$).

For surgical treatment of pancreatic cancers, successful and suitable AC has become a key factor to achieve better overall survival, and this fact has been proved by reliable randomized prospective trials (*4,5*). However, these recent trials included patients with a good postoperative course, which allowed patients to match the eligibility criteria to undergo the planned regimen of AC set for trials. To date, however, the factors for the failure to complete or introduce the AC have not been fully elucidated. Aoyama *et al*. have recently reported that a creatinine clearance (CCr) < 60 mL/min was a significant risk factor for the discontinuation of S-1 AC, even though the renal function was judged to be normal based on the serum creatinine level (*19*). Otherwise, lower preoperative prognostic nutritional index (PNI) level, intraoperative blood transfusion, and organ and/or space SSI were critical risk factors for the failure to complete AC. Based on these backgrounds, we analyzed the various preoperative factors to predict the failure to complete AC. As a result, age, sarcopenia, preoperative CEA, creatinine clearance and tumor size were found to be potential risk factors for the failure to complete AC. Furthermore, multivariate analysis indicated that age ≥ 70 years and sarcopenia were significantly independent factors. Therefore, relatively poor preoperative patient condition may be importantly associated with the tolerability of chemotherapy after pancreatic resection. In addition, preoperative CEA and tumor size seems to be important critical risk factors for the failure to complete AC. One possible estimation of this result indicates that more advanced tumor status causes the more deteriorated patient status and poorer nutrition deprived by the tumor-associated burden, which leads to poor tolerance of AC.

As for relation between achievement of adjuvant therapy and age, our series included only 2 patients who failed to complete AC when stratified under 70 years old, and rate of sarcopenia in patients of 70 years old or younger was significantly lower than that in patients over 70 years old (15% *vs*. 38%, $p < 0.001$). Therefore, sarcopenia seems to have insignificant impact on AC in patients under 70 years old. On the other hand, sarcopenia had significantly negative impact on successful AC in patients over 70 years old. We expect

that evaluation of sarcopenia would be useful to predict the risk of failure in AC after PD for PC patients over 70 years old.

As shown in the Results, each laboratory datum of patient's background could not predict the failure risk of AC. Sarcopenia may reflects systemic tolerance ability for burden of surgery or chemotherapy and could be used as a good surrogate to predict the tolerability for multidisciplinary treatment for PDAC. Other possible speculation is that BSA of patients with sarcopenia may be overestimated. Since the dose intensity of AC is usually determined based on BSA, patients with sarcopenia might have undergone rather overdosed chemotherapy, which might have negative impact on continuance of AC. Due to limited number of patients of the current series, we didn't demonstrate significant difference of adverse events of AC between two groups, which should be investigated in future larger series.

As for long-term survival, sarcopenia showed significant impact on overall survival. However, survival after resection of PDAC is affected by not only patient's factors but also by tumor state. In our result, tumor size and CEA tended to be greater in sarcopenia group than those in non-sarcopenia group, although statistical significance was not proved. Further accumulation of patient number is needed to clarify the confounding of these factors.

It is critically important to examine if the suitable nutritional or immunologic support can improve patient condition and enhance the completion rate of planned AC. According to recent guidelines (*20*), it is recommended to evaluate the patient nutritional status since the beginning of treatment and to carefully control it throughout the treatment. Although many studies addressed the nutritional assessment or intervention on cancer patients, there are few studies about the perioperative nutritional support for the PC patients receiving curative-intent treatments. Since this issue becomes more important especially in the era of the multidisciplinary treatment, further prospective studies are clearly required.

This study has some limitations. Firstly, due to limited number of patients in single-center retrospective analysis, our results would be influenced by bias. Secondly, our retrospective data lacks preoperative trends of body weight or oral intake status, which would hamper to distinguish the reason of sarcopenia, for example, dietary habits or deterioration by malignant disease. Thirds, our study population mainly includes patients who underwent upfront resection. Therefore, results of our study should not be simply generalized in the modern era of neoadjuvant therapy for PC.

In conclusion, age and sarcopenia were significant risk factors for the failure to more than 6 months of adjuvant chemotherapy. Especially in elderly patients, sarcopenia has critical impact on AC, and preoperative physical and nutritional intervention to resolve sarcopenia should be considered.

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An expanded view of infertility: The challenge of the changing profiling of major birth defects in China

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SUMMARY Over the past two decades, China has experienced a significant decline in birth rates, accompanied by a decrease in fertility and changes in major congenital defects. The development of assisted reproductive technology (ART) has brought hope to individuals facing infertility. However, some issues related to reproductive health and congenital defects have arisen. The reasons for the changing profiling of birth defects and the relationship between the decline in fertility and ART need to be further investigated. Lifestyle factors such as nutritional supplementation need to be altered to protect reproductive capacity. Birth defects, such as congenital heart defects and hypospadias, may serve as a signal for understanding the decline in fertility. To improve fertility, the factors contributing to it need to be identified, vital genetic and medical technologies need to be introduced, and environmental interventions, such as nutritional changes, need to be implemented.

Keywords assisted reproductive technology (ART), infertility, birth defect, hypospadias, congenital heart defects

Over the past two decades, China has undergone significant changes in the structure of its population, with a decline in birth rates from 14‰ to 6.8‰ (Figure 1A) and an acceleration of aging. At the same time, there has been a notable decrease in the incidence of severe birth defects during the perinatal period, such as neural tube defects (NTDs) (Figure 1B). However, the fact that the prevalence of infertility among couples of childbearing age in China has increased to 25% is concerning (*1*). Advances in assisted reproductive technology (ART) have led to a significant demand for surrogacy, resulting in the emergence of a substantial underground market driven by infertile individuals seeking to fulfill their desire for parenthood (*2*). The fact that factors such as age, environmental exposure, lifestyle, and pathophysiological factors contribute to infertility is evident (*3*), but it is the obligation to be aware of several critical aspects of reproductive health related to birth defects.

First, the prevalence of major birth defects has changed, accompanied by a decline in fertility. In 2020, the ten most prevalent birth defects during the perinatal period were congenital heart disease (CHD), polydactyly, syndactyly, hypospadias, clubfoot, total cleft lip, cleft palate, rectal anal atresia or stenosis, hydrocephalus, and microtia (Figure 1B). The prevalence of NTDs and limb shortening has significantly declined, and the two no longer rank among the ten most prevalent birth defects. CHD ranked as the most prevalent birth defect, while polydactyly has consistently been the second most prevalent since 2000. Syndactyly and hypospadias, in contrast, have respectively risen from the ninth and eighth most prevalent birth defect in 2010 to the third and fourth most prevalent in 2020. The prevalence of CHD, polydactyly, syndactyly, hypospadias, and clubfoot in 2020 was significantly higher than in year 2000, with the prevalence CHD increasing 15.2-fold, that of polydactyly increasing 1.9-fold, that of syndactyly increasing 2.0-fold, that of hypospadias increasing 1.6-fold, and that of clubfoot increasing 1.1-fold. In a recent retrospective cohort study involving 507,390 singleton or twin pregnancies, the prevalence of CHD was found to be higher in pregnancies assisted by reproductive technology compared to non-assisted pregnancies (adjusted odds ratio: 1.70, 95% confidence interval: 1.48-1.95) (*4*). The etiology of CHD is multifactorial (*5*), indicating the involvement of multiple genetic and environmental factors that interact

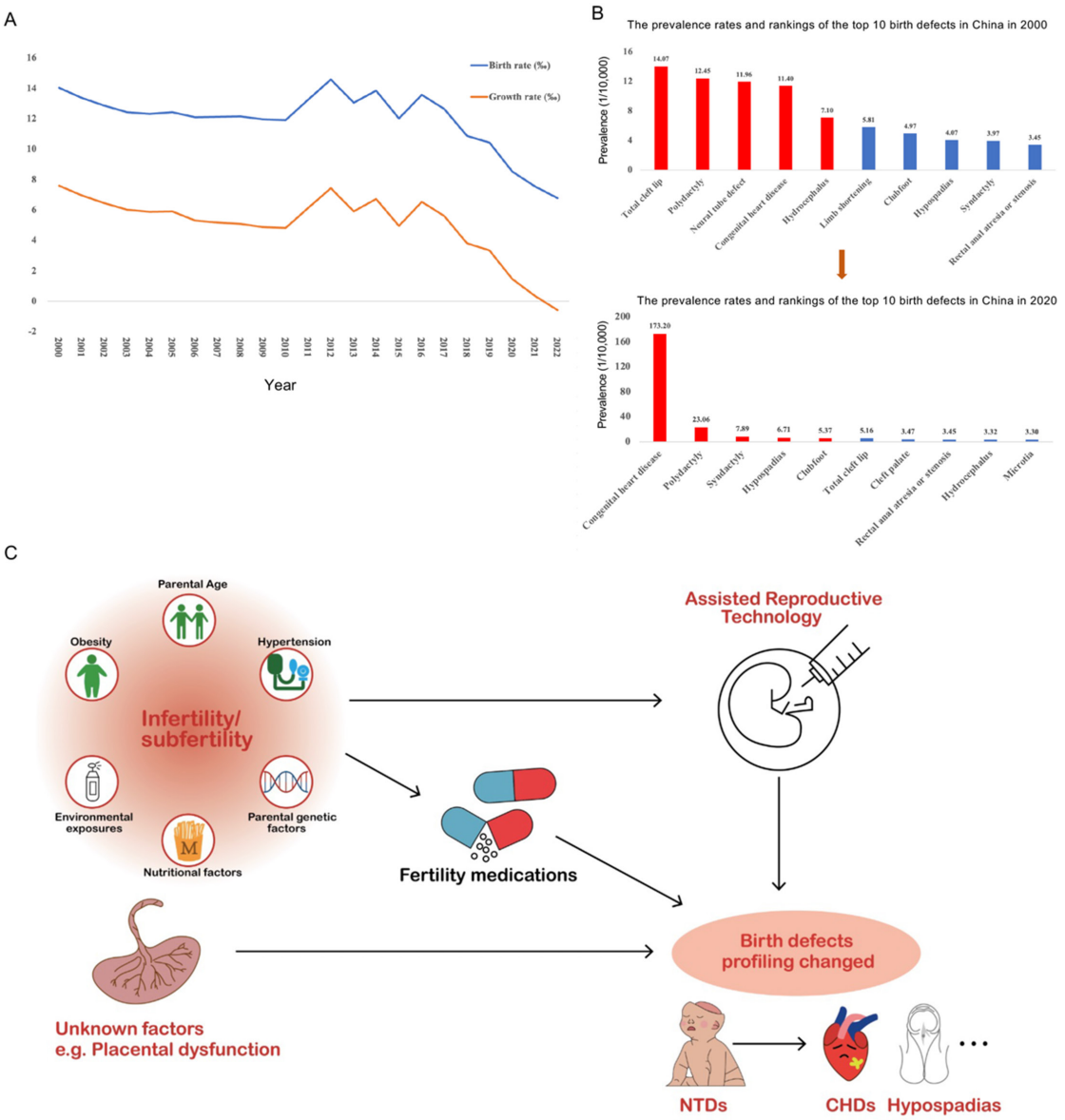

Figure 1. The changing trends in birth defects in China and the potential causes of an increase in specific birth defects. (A) Changes in the birth rate and growth rate, from 2000 to 2022 in China. **(B)** The changing prevalence and rankings of the top 10 birth defects in China in 2000 and 2020. **(C)** The potential multifactorial etiology of an increase in the specific birth defects associated with infertility and assisted reproductive technology.

with each other. Confounding factors, such as maternal age, fertility medications, and placental dysfunction, appear to play a crucial role in determining the increased risk of CHD. However, further evidence is necessary for a precise assessment of the actual risk. Men with hypospadias have a reduced likelihood of fathering biological children due to impaired fertility, leading to an increased reliance on ART and a higher risk of being diagnosed with male infertility (*6*). Overall, the changing prevalence of major birth defects and the association between ART and impaired fertility in men with hypospadias highlight the complex dynamic relationship between reproductive health and birth outcomes and the need for comprehensive research and interventions in this field.

Second, nutritional supplementation plays a role in influencing the types of major birth defects. Findings from years of animal and human studies have revealed that the vast majority of birth defects have multifactorial origins, with contributions from environmental exposure and inherited genetic factors. Environmental exposure refers to kinds of non-genetic factors that disrupt the normal developmental process during intrauterine life. These factors encompass exogenous elements (such as metallic elements, air pollutants, and pesticides), substances consumed during early pregnancy (alcohol, drugs, smoking, *etc.*) and maternal nutritional status (folic acid (FA), inositol, choline, Vitamin B12, *etc.*). Despite the reduction in the prevalence of NTDs due to the introduction of FA supplementation during pregnancy by

the Chinese Government (*7,8*), the changing landscape of birth defect types presents new challenges. A decrease in fertility is mainly dependent on the low quality of female and male gametes. Metabolic levels of the nutrient inositol were reported to ensure the proper functioning of male and female reproductive cells, and impaired or abnormal levels in follicular fluid (FF) or semen are frequently associated with pathological features and reduced fertility (*9,10*). Encouraging proper nutrition and supplementation, with supplements such as inositol, that positively impact the reproductive system can improve fertility rates to ensure safe embryo formation and fetal development.

Further elucidation is needed to understand the genetic causes and underlying mechanisms that contribute to infertility associated with CHD and hypospadias. A recent large prospective cohort study involving 38,528 postmenopausal women found that infertility is associated with an increased risk of overall heart failure in the future (*11*). ART offers hope to infertile patients, but the transmission of infertility-associated variants to future generations is a concern. The analysis of genetic factors influencing infertility holds significant promise in providing valuable insights into the development of targeted treatments for patients and unraveling the causes of idiopathic infertility. The multifactorial inheritance of CHD and hypospadias suggests a significant genetic component contributing to the risk of these birth defects (*5*). The association between 37 transcription factor (TF) genes and CHD and hypospadias suggests their critical role in these conditions, where a stable equilibrium network governed by TF expression contributes to robustness (*5*). Emerging sequencing technologies that offer a global perspective on genetic analysis have the potential to advance our understanding of the etiology of infertility by genetically profiling CHD and hypospadias associated with infertility. Over half of the genes responsible for CHD that have been identified through whole-exome sequencing (WES) are associated with ciliopathies in mouse models (*12*). Moreover, damaging variants of ciliary genes were found to be enriched in patients with transposition of the great arteries (TGA) (*13*), a complex congenital heart defect. Chen *et al*. reported that knock-out of the *Dnah8* gene causing hypospadias resulted in decreased testosterone levels in male mice and failure to produce offspring (*14*). These results further substantiate the established link between ciliary function and CHD, hypospadias, and infertility. In addition, rare diseases affecting the endocrine and reproductive systems, such as disorders of sex development (DSD), androgen insensitivity syndrome (AIS) (*15*) and urogenital sinus malformation (*16*), can also have implications for fertility and warrant attention.

The changing trends in birth defects in China and the prevalence of infertility pose a significant medical concern, and yet the mechanisms underlying infertility are still poorly understood. The rising prevalence of infertility has driven an increased demand for ART. Birth defects, including CHD and hypospadias, may serve as an early warning signal for reproductive health issues in the broader population. Preimplantation genetic diagnosis and appropriate nutritional supplementation are crucial, particularly for individuals with a family history of infertility. To improve fertility, factors contributing to it need to be identified, vital genetic and medical technologies need to be introduced, and environmental interventions, such as nutritional changes, need to be implemented in the future.

Data availability: The birth rate and growth rate data (from 2000 to 2022 in China) are available from the National Bureau of Statistics of the People's Republic of China (*http://www.stats.gov.cn/sj/*) (in Chinese). The prevalence and rankings of the top 10 birth defects in China in 2000 and 2020 are available from the Maternal and Child Health Surveillance of China (*https://www.mchscn.cn*) (in Chinese).

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The framework for modern community medicine in Japan

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SUMMARY Along with the transition to depopulation and an aging society in Japan, the modification of community medicine and its related systems is required. With this in mind, the Japanese government has recently advocated two major plans: 'Community Healthcare Vision' and 'Community-based Integrated Care System'. This paper proposes a theoretical framework to understand modern community medicine based on the ongoing government plans. The key viewpoints consisting of the framework are 'community and/or region', 'care systematization,' and 'coworking with residents (citizens)'. This is expected to be useful for capturing and monitoring the whole picture of modern community medicine in Japan. Such modeling might aid in the future development of medicine and medical science, as in other developed countries.

Keywords community health, community coalition, healthcare system, medical care, medical model

1. Introduction

Community medicine is a special branch of the medical science of health and disease in a defined community and/or region, often dealing with the fields of primary healthcare and healthcare delivery systems in addition to clinical practice for outpatients and inpatients (*1,2*). Community medicine depends on not only the progress of medical care and related technologies but also the characteristics of the respective communities and/or regions.

While the human lifespan has been prolonged in Japan (mean life expectancy of about 81 years for men and 87 years for women in 2017 (*3*)), the country has experienced depopulation (population decline from 128 million after 2008) and population aging as a super-aged society (older people accounted for over 27% of the population in 2018) (*3-6*). This societal transition leads that of other developed countries around the world (*7*).

In general, older people have chronic diseases with multiple comorbidities and have difficulties in remaining mobile in their daily life and obtaining access to medical care (*7*); long-term care should thus be available in their local area, ideally. Depopulation with a decline in the working-age population may also result in a shortage of human resources working in medical care facilities (*8*). Accordingly, these will accelerate the need to reconceptualize the notion of community medicine and to restructure its related systems.

2. Government plans for community medicine

Recently, the Japanese government proposed two plans to reform community medicine in the near future. The first plan is the 'Community Healthcare Vision' (*6*), established based on data concerning medical demands and bed numbers required, with hospital beds differentiated by the required functions (*i.e.*, advanced acute phase, acute phase, convalescence phase, and chronic phase functions) in certain regions at the prefecture level. Hospitals in Japan tend to serve the functions of an advanced acute-phase or acute-phase institution, as they were established when the population was younger than in the present day. With the increased aging of the population, hospitals could be converted to cover their functions in the convalescence or chronic phase. Such conversion should match the characteristics of a given region (*e.g.*, aging rate, hospital bed numbers), and integrative cooperation is also necessary to balance the functions among hospitals within respective regions.

The second plan is the 'Community-based Integrated Care System' (*3,5*). This system ensures the provision of health and medical care, nursing care, prevention, housing, and livelihood support for daily living in certain communities at the municipal level. Diverse components, such as clinics for home medical care, home-visit nursing stations, welfare-related administrative organizations, informal services, and self-help groups, will also join the system. This plan is aimed at realizing that most people live in their familiar community for a long time. Comprehensive care should be instated to improve life for everyone, particularly older individuals, and integrative cooperation between stakeholders within

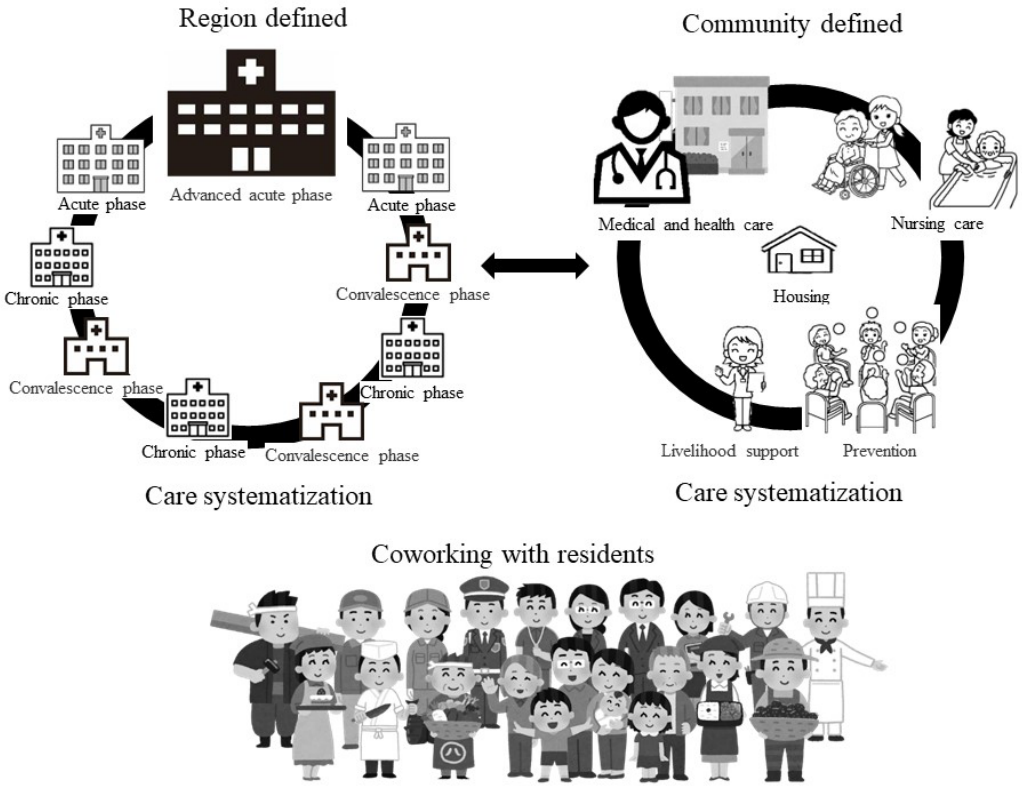

Figure 1. The framework of modern community medicine (image). The government plans as the 'Community Healthcare Vision (left circled-figure)' and 'Community-based Integrated Care System (right circled-figure)' are involved in the framework. The key viewpoints consisting of the framework are 'community and/or region', 'care systematization', and 'coworking with residents (citizens)'.

respective communities is a must-have. Of note, it is also important to harmonize these two plans 'Community Healthcare Vision' and 'Community-based Integrated Care System' for community medicine.

3. Framework for modern community medicine based on the government plans

These plans are relatively new, and their developing while dealing with a wide range of issues is ongoing (*3,5,6*); thus, it is often difficult for people to understand the whole picture. A framework may be useful for capturing the essence of modern community medicine. Here, the author would like to propose the framework shown in Figure 1, keeping the two above-mentioned plans in mind.

First, we must define the 'community and/or region', which will make it easy to catch up the detailed characteristics (*i.e.*, population demographics, disease structures, human resources, and facilities) for the plans. Second, we must look at 'care systematization'. Following these plans, it is crucial to combine human resources and facilities fully. For instance, objective measures using big data from medical care- and long-term care-related receipts as well as evidence-based clinical indicators obtained from facilities can be utilized to assess and promote the care systematization required in communities and/or regions (*9*). Both technical and non-technical approaches for the management and governance of interprofessional collaboration between resources should also be utilized (*10*). Third, we must focus on 'coworking with residents (general people)'. The relevance of participation, involvement, coalition, and engagement of residents living in communities and/or regions has been recognized as a factor associated with the successful penetration of community medicine policies and actions (*11,12*). The plans will not proceed without the partnership of residents with care professionals and administrators. For example, we recognize the importance of achieving a consensus on drastic challenges involving the functional arrangements of hospitals and working closely with medical and welfare care in cases of advanced end-of-life planning (*13*). Recently, a method to facilitate the sharing of information and/or intention via digital transformation using communications technology has been proposed (*14,15*).

4. Conclusions

Insights into modern community medicine can be discussed from the viewpoint of the framework, as presented here, in the context of Japan. The key viewpoints are 'community and/or region', 'care

systematization', and 'coworking with residents'. We can verify the status of community medicine in the respective communities and/or regions by considering these viewpoints. The application of the framework to community medicine may help enhance care and maintain the sustainability of care while ensuring the safety of people within communities and/or regions. The Japanese models of modern community medicine with quantitative and qualitative alterations in society might aid in the future development of medicine and medical science, as in other developed countries.

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BioScience Trends will perform an especially prompt review to encourage innovative work. All original research will be subjected to a rigorous standard of peer review and will be edited by experienced copy editors to the highest standards.

Ethical Approval of Studies and Informed Consent: For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. When your manuscript contains any case details, personal information and/or images of patients or other individuals, authors must obtain appropriate written consent, permission and release in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. The consent form needs to comply with the relevant legal requirements of your particular jurisdiction, and please do not send signed consent form to *BioScience Trends* to respect your patient's and any other individual's privacy. Please instead describe the information clearly in the Methods (patient consent) section of your manuscript while retaining copies of the signed forms in the event they should be needed. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Reporting Clinical Trials: The ICMJE (*https:// icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html*) defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Registration of clinical trials in a public trial registry at or before the time of first patient enrollment is a condition of consideration for publication in *BioScience Trends*, and the trial registration number will be published at the end of the Abstract. The registry must be independent of for-profit interest and publicly accessible. Reports of trials must conform to CONSORT 2010 guidelines (*https://consort-statement.org/consort-2010*). Articles reporting the results of randomized trials must include the CONSORT flow diagram showing the progress of patients throughout the trial.

Conflict of Interest: All authors are required to disclose any actual or potential conflict of interest including financial interests or relationships with other people or organizations that might raise questions of bias

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Submission Declaration: When a manuscript is considered for submission to *BioScience Trends*, the authors should confirm that 1) no part of this manuscript is currently under consideration for publication elsewhere; 2) this manuscript does not contain the same information in whole or in part as manuscripts that have been published, accepted, or are under review elsewhere, except in the form of an abstract, a letter to the editor, or part of a published lecture or academic thesis; 3) authorization for publication has been obtained from the authors' employer or institution; and 4) all contributing authors have agreed to submit this manuscript.

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The manuscript must be accompanied by a cover letter prepared by the corresponding author on behalf of all authors. The letter should indicate the basic findings of the work and their significance. The letter should also include a statement affirming that all authors concur with the submission and that the material submitted for publication has not been published previously or is not under consideration for publication elsewhere. The cover letter should be submitted in PDF format. For an example of Cover Letter, please visit: *https://www.biosciencetrends.com/downcentre* (Download Centre).

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6. Manuscript Preparation

Manuscripts are suggested to be prepared in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals", as presented at *https://www.ICMJE.org*.

Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (*e.g.* DNA). Single words should not be abbreviated.

Title page: The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; 5) author contribution statements to specify the individual contributions of all authors to this manuscript, and 6) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state "There is no conflict of interest to disclose").

Abstract: The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, News, or Letters, a brief summary of main content in 150 words or fewer should be included in the manuscript. For articles reporting clinical trials, the trial registration number should be stated at the end of the Abstract. Abbreviations must be kept to a minimum and non-standard

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Examples are given below:

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Inagaki Y, Tang W, Zhang L, Du GH, Xu WF, Kokudo N. Novel aminopeptidase N (APN/CD13) inhibitor 24F can suppress invasion of hepatocellular carcinoma cells as well as angiogenesis. Biosci Trends. 2010; 4:56-60.

Example 2 (Sample journal reference with more than 15 authors):

Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: Collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

Example 3 (Sample book reference):

Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

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World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_ en.pdf* (accessed September 23, 2022).

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