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Frailty and frailty syndrome – one of the causes and effects of cardiovascular diseases in the geriatric population

Mikołaj Młyński, Krzysztof Młodziński, Justyna Rohun
Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland

Abstract

Frailty syndrome is described as a clinical condition in which the functional reserves of the body are reduced due to progressive disruption of homeostasis. It is caused by the overlap of a critical number of changes related to the ageing process, changes due to genetic predisposition and changes related to psychosocial and somatic conditions. The frailty syndrome is closely linked to the incidence of cardiovascular disease and increases the risk of associated complications. It affects not only the prognosis, but also the management of cardiovascular disease prevention and treatment in the geriatric population. It is important to pay attention to this relationship in the provision of comprehensive geriatric care for elderly patients. *Geriatria 2022;16:206-212. doi: 10.53139/G.20221633*

Keywords: frailty, cardiovascular disease, coronary disease, heart failure, arrythmia, geriatric population

Introduction

Frailty is defined as a clinical condition resulting in an increased vulnerability to endogenous and exogenous stressors, as an effect of age-related decline in reserve and function of multiple physiologic systems [1,2]. The incidence of frailty increases with age, which is of major importance in ageing populations. Frailty is an indicative of a broader, clinical term – frailty syndrome (FS). The general characteristics of FS include: weight loss, weakness, fatigue, exhaustion and slowness – all defined by criteria developed based on the data obtained in the Cardiovascular Health Study (CHS) [3]. On average, in the European countries, frailty affects up to 18% of people over 65 years [1,4]. The risk of developing frailty syndrome is affected by environmental factors, malnutrition, metabolic disorders, physiological impairment within organism's systems and chronic diseases. Some of the most significant risk factors for FS relate to the cardiovascular system, including heart failure, peripheral vascular disease, previous myocardial infarctions and strokes. Moreover, the coincidence of frailty syndrome affects the prognosis of patients with cardiovascular diseases, causing increased mortality due to both cardiovascular (CV) diseases and all-cause mortality [1]. Thus, it is necessary to highlight and summarize the interconnection between frailty syndrome and cardiovascular diseases.

Methods

We systematically searched Pubmed for the literature from 2000 to November 2022. The keywords were "geriatric population", "frailty", "pathophysiology of frailty syndrome", "cardiovascular disease", "coronary syndrome", "heart failure", "arrhythmia" and "atrial fibrillation". Among the findings, most up-to-date observational studies, randomized controlled trials, systematic reviews and meta-analysis were selected.

Causes and pathophysiology of frailty syndrome

The development of frailty is multifactorial, rooting from various changes occurring in the ageing patients. These factors can be divided into: age-related changes in organism's functioning, genetic predisposition, factors related to nutritional status, lifestyle and the effects of chronic diseases and additional stress factors, such as acute conditions. The overlapping of these changes results in dysregulation of immune, endocrine, nervous and cardiovascular functions, the development of chronic inflammation, leading to increased vulnerability to future disease phenomena [5].

Ageing-related changes and genetic predisposition

Body function deteriorates with age at many levels, including cellular, tissue and systemic. The main age-related factors involved in the development of frailty syndrome are mitochondrial dysfunction, cellular ageing, stem cell decline and impaired cell autophagy.

It is also grounded in the changes that occur with ageing in the genetic material of cells, most notably telomere shortening and progressive DNA damage and disruption of its methylation [6-8].

Changes related to the nutritional status and lifestyle

Both the nutritional status of the elderly and the lifestyle of patients in the preceding decades have an impact on the development of frailty syndrome. Nutritional status is primarily responsible for metabolic reserves, proper function and endurance of the musculoskeletal, endocrine and other systems. Factors associated with the development of frailty syndrome include both malnutrition and obesity. Malnutrition can be a factor in causing changes that fall under all the criteria of physical frailty - loss of muscle strength, weight loss, slowing down, weakness and decreased physical activity. Analogous to frailty syndrome itself, malnutrition is associated with increased morbidity, higher frequency of hospital admissions, higher frequency of outpatient visits and increased dependency. Obesity as a risk factor for frailty syndrome most often occurs together with reduced muscle mass, and the risk of developing frailty syndrome increases with the duration of obesity over a lifetime. Diet and nutrition also influence the regulation of inflammatory processes in the body and the occurrence of oxidative stress [8].

Lifestyle, irrespective of nutritional status, is responsible for both the predisposition to develop chronic diseases and the functioning of individual systems. Exposure to harmful factors, e.g. smoking, alcohol abuse, and insufficient physical activity influence both the occurrence of cardiovascular and nervous system diseases, but also cause dysregulation of the immune system and have a pro-inflammatory effect.

Changes related to chronic disease and comorbidities

The higher prevalence of chronic diseases is closely linked to the presence of frailty syndrome. Some of the main risk factors include cardiovascular diseases: a history of myocardial infarction, heart failure, atherosclerosis, hypertension, strokes, but also others such as diabetes, chronic kidney disease and chronic obstructive pulmonary disease.

Pathophysiological effects

The pathophysiological effects of frailty syndrome primarily include dysregulation of the immune, endocrine, nervous and cardiovascular systems. In the immune system, there is a shift in balance towards pro-inflammatory responses, which is represented by an increase in pro-inflammatory cytokines such as IL-1, IL-6, TNF-alpha and inflammatory markers. This results in increased catabolism and dysfunction in terms of other systems. In the endocrine system, the hypothalamic-pituitary-adrenal axis is disrupted, resulting in increased cortisol and decreased anabolic hormones. This leads to an increase in catabolism and a decrease in muscle mass, resulting in impaired performance and reduced muscle strength. Another effect of the above changes is the development of insulin resistance and impaired carbohydrate metabolism. In addition, less ghrelin and growth hormone are produced, which reduces appetite and increases the predisposition to malnutrition. Increased inflammatory processes are also a risk factor for cardiovascular disease [9].

Reduced muscle mass results in reduced energy requirements and a slower metabolic rate, which, combined with reduced appetite, further exacerbates protein malnutrition. This relationship creates a closed cycle of escalating disorders, leading to a continued increase in frailty in those at risk and those already affected.

Clinical implications of frailty

As stated by Fried et al. frailty is considered to be a condition highly predictive of adverse health outcomes. It is associated with significantly increased risk of mortality, as well as hospitalizations, falls together with worsening mobility and disability within activities of daily living (ADL) [2].

In the study conducted by Fried et al. patients with frailty had over 3-fold higher risk of all-cause mortality within 7 years of observation when compared to their non-frail counterparts. FS has been proved to be an independent risk factor of the aforementioned outcomes with HR between 1.23-1.79 within 7 years of observation, excluding falls. Moreover, in the same study, it has been shown that intermediate level of frailty increased the risk of developing frailty syndrome over 3 years almost 3-fold when compared to non-frail patients [1].

As stated by Rockwood, mild as well as moderate and severe frailty has been associated with a higher risk of institutionalization when compared to non-frail elderly patients.

Frailty syndrome in cardiovascular diseases

In a meta-analysis conducted by Veronese et al., which included 31,343 older participants, it has been shown that frailty and pre-frailty were associated with both increased risk of any cardiovascular disease and a ~3-fold higher risk of death due to CV causes [10].

The relationship between frailty and specific cardiovascular diseases differs and affects the management and prognosis of patients. It requires certain measures for optimal management of symptoms and treatment. The CV diseases for which the frailty models have been described specifically include: chronic coronary syndrome, arrhythmias, valvular heart diseases, chronic heart failure and peripheral vascular disease.

Chronic coronary syndrome (CCS)

There is a high prevalence of advanced and multivessel coronary artery disease (CAD) in patients ≥80 years old[11]. Chronic coronary syndrome is the major mortality risk factor in elderly patients and it is significantly more likely for patients with frailty syndrome to suffer from acute coronary events. What is more, geriatric and frail patients are more likely to present atypical symptoms of significant CAD. The choice of treatment in elderly frail patients with CCS is affected by the increased risk of complications after surgical interventions and heart catheterization. Frailty in not well represented in the risk assessment models for cardiosurgical procedures – the only directly related factor included in the Euroscore II system is poor mobility [12]. This decreases the chance of benefit from invasive procedures in this group of patients [13]. Major complications are related to bleeding, due to the use of antiplatelet drugs, the choice of vascular access, post-procedural myocardial infarctions and infections. Post-procedural complications may cause overall health deterioration due to progression of frailty.

In frail patients subjected to percutaneous coronary intervention (PCI), the mortality risk in 3-year observation period was more than 4-fold higher than in non-frail patients, according to Singh et al. (28% vs 6% risk) [14]. In a study conducted by Freiheit et al., which compared pharmacotherapy, PCI and coronary artery bypass grafting (CABG), the last was shown to cause the highest frailty progression in patients with CAD [15].

Valvular heart disease (VHD)

The most performed surgical valvular procedures are the aortic valve replacement (AVR) and mitral valve repair (MVR). Such procedures can be performed via a standard surgical access or transcatheter access, with the latter, less invasive procedure being more adequate for patients with increased peri-operative risk rates.

Recent studies have proved that severely frail elderly patients are subjected to functional decline or lack of improvement after transcatheter aortic valve repair (TAVR) and surgical aortic valve repair (SAVR), as stated by Kim et al. [16] however the authors did not compare the results between these approaches. Recognizing frailty has become an increasingly important checkpoint in the patient qualification process. Kundi et al. have shown that in transcatheter valve repair procedures of both aortic and mitral valves, the increasing severity of frailty correlated with 1-year mortality rates, using the Hospital Frailty Risk Score calculator. In TAVR the 1-year mortality rates for patients with low, intermediate and high-risk were 7.6%, 17.6% and 30.1% respectably, while in transcatheter mitral valve repair the rates were 12.8%, 29.7% and 40.9% respectably, with $p < 0.001$ in both patient cohorts [17]. In a study conducted by Shibata and colleagues, the researchers have proved a correlation between Geriatric Nutritional Risk Index (GNRI) and FS components such as gait speed, grip strength and Clinical Frailty Scale. The GNRI value correlated also with Society of Thoracic Surgeons (STS) score. Such findings show that GNRI may be assessed as an indirect predictive factor of worse outcomes after surgery [18]. Moreover, during the prospective multicenter cohort study FRAILTY-AVR in which patients over 70 years old were assessed using Mini Nutritional Assessment Short Form and Short Performance Physical Battery scores, it was that preoperative nutrition status could have predictive value in assessing 1-year mortality rates post-AVR [19]. However, as mentioned in the meta-analysis conducted by Li et al., the frailty assessment instruments in the current studies are potentially useful, yet varied, creating a need for systematized preoperative assessment of frailty and its risks [20].

It is crucial for the Heart Team to assess the patient according to the Euroscore II system and recognize the signs of frailty using aforementioned scales and scoring systems, while qualifying the patients for the valvular procedure, in order to minimize the chance for frailty progression and perioperative complications.

Chronic Heart Failure (CHF)

The incidence of frailty among HF patients is high, ranging from 30 to 52%, however different assessment methods of FS show slight differences in the prevalence of this syndrome within this population. According to Denfeld and colleagues, the use of Multidimensional Frailty measures provides a higher incidence of FS in subjects with heart failure, when compared to Physical Frailty measures [21,22]. This may suggest that frailty in patients with HF is more related to the pathophysiology and biological effects of the disease, than in other CVDs. However, frailty is still associated with increasing age and the number of comorbidities among patients with heart failure. In terms of screening patients with chronic HF, Sze et al. have shown that Clinical Frailty scale has the greatest correlation with the examination performed using frailty assessment tools, such as Fried criteria [22].

Presence of frailty among patients with HF can be associated with all-cause mortality, exacerbation of disability and more frequent hospitalizations, including hospital readmissions and first unplanned hospitalization due to HF after diagnosis [23-25]. As described in the meta-analysis by Yang and colleagues, frailty in chronic HF patients increases the mortality rates and hospitalization rates ~1.5-fold ($p < 0.001$) [25]. Similarly, Zhang et al. have shown that, FS significantly increased the risk of mortality of all causes and hospitalizations by ~60% ($p <0.001$) and ~30% ($p <0.001$) respectably. Moreover, the study results state that frailty is predictive of all-cause mortality after implantation of ventricular assist device (HR = 1.62, $p <0.001$) [23]. What is more, in the prospective multicenter cohort study FRAGILE-HF, Matsue et al. have assessed patients over 65 years old with HF diagnosis in terms of physical frailty, social frailty and cognitive dysfunction, showing that patients with frailty identified in ≥2 of above domains were at higher risk of 1-year mortality from all causes and rehospitalization than their non-frail counterparts [26].

It is crucial in patients with heart failure, to prevent and address the existing FS, in order to reduce the incidence of negative outcomes. As stated in a systematic review by Aili et al., there is a potential for frailty prevention and reversion, at least partially, by introducing prehabiltation and rehabilitation programs. In a review by Bjarnason-Wehrens et al. it is stated that resistance training may be applied, however data on its effectiveness and safety among frail patients is limited [27]. However, in a recent review Sunayama and colleagues mention that there is little data on addressing social frailty, which is the most common domain of frailty reported among HF patients [28].

Arrhythmias

The most common chronic and sustained arrhythmia in the elderly population is atrial fibrillation (AF). It is also more often concomitant in patients with other chronic diseases, such as hypertension, heart failure, diabetes, chronic kidney disease, cancer, COPD or inflammatory diseases. Sustained atrial fibrillation is associated with a higher incidence of cognitive and physical deterioration. As shown in the Health ABC study, patients with AF suffered from a significantly greater decrease in 4-year physical performance battery decline, in terms of grip strength, walk distance and walk time, when assessed four times between the ages of 70 and 82 years [29]. Frailty is also strongly associated with negative outcomes in patients with AF. In a national prospective cohort study conducted by Gugganig et al. in Switzerland, the authors proved that pre-frailty and frailty significantly increased the risk of unplanned hospitalizations, all-cause mortality and bleeding in AF patients. FS also correlated with higher risk of stroke [30]. In a recent systematic review and meta-analysis by Proietti and colleagues, based on data of over a million AF patients, frailty was associated with a greatly increased risk of mortality of all causes, ischemic stroke and bleeding.

Regardless of frailty status, patients with AF may be subjected to different treatment strategies – rate control or rhythm control, which tend to provide different outcomes in terms of long-term prognosis. There is a correlation between the application of rate control strategy and 1-year mortality, stroke and cognitive degeneration, proving possible benefits of introducing rhythm control strategy [31,32].

In terms of electrotherapy, patients with AF may be subjected to direct-current external cardioversion (ECV) or catheter ablation (CA). A retrospective study on the effectiveness of ECV in patients with AF conducted by Fumagalli et al. showed no clinical significance of age in relation to AF relapse within an average ~3-year observation period. In studies lead by Hsieh et al. and Nademanee et al., CA therapy for AF has been shown to significantly decrease the incidence of mortality, stroke or hospitalizations in elderly patients with prior AF [33,34]. These findings are partially supported

by the CABANA randomized clinical trial, in which CA was compared to antiarrhythmic drug therapy [35]. The researchers have shown a significant decrease in secondary end points of death or CV hospitalization (HR 0.83, $p = 0.001$) an AF recurrence (HR 0.52, $p < 0.001$) in the former intervention group.

Hence, as suggested by Fumagalli and colleagues, based on the EHRA survey [36] on multidisciplinary approach to cardiac arrhythmias, patients with AF should be referred for most optimal treatment according to their current health, comorbidities and expected trajectory of overall well-being rather than based on their age – elderly patients should be initially eligible for all variants of treatments.

Management of frailty – focus on cardiovascular diseases

Decreasing the impact of frailty of the individual should be attempted by detecting patients at risk of frailty and at pre-frailty stage, who will most likely benefit from early interventions. Plenty of screening tools, as some mentioned above, have been developed to provide the most comprehensive assessment of patient's physical and psychosocial parameters, yet there is no single optimal scale or scoring system dedicated towards early diagnosis of frailty and FS. It is even more complex, when taking into consideration CV patients, where the comorbidities specifically affect different dimensions of frailty.

In patients who are at risk of frailty or show signs of frailty in any dimension of life, comprehensive geriatric assessment or identification of domains affected by frailty should be performed. As there is no specific treatment for frailty and frailty syndrome, it is necessary to address the modifiable and reversible deficits. Any intervention should be suitable for the certain individual, their lifespan prognosis and possible treatment options of chronic diseases.

Most important aspects of management of frailty in patients with CV diseases include nutrition, exercise and interventions such as providing dental care or cognitive training. The aim of these interventions is to address the dietary deficiencies, prevent the loss of muscle mass and avoid mental deterioration. What is more, it is vital to avoid possibly harmful practices. Specifically in geriatric population, patients are at hazard of polypharmacy and prolonged hospitalizations.

In addition, cardiac rehabilitation should be available after acute CV events and pre-rehabilation should be considered before scheduled interventions. Frailty, especially in special groups of patients should be assessed and treated by a multidisciplinary team of specialists, including cardiologists, cardiac surgeons, general practitioners, geriatricians, nurses and nutritionists [37-39].

Conclusions

Frailty and frailty syndrome still pose a great difficulty in managing patients with cardiovascular diseases, although there are more tools and treatment programs being developed. Further research into assessment of frailty and correlation between FS and cardiovascular health is necessary. However, current discoveries prove that geriatric and frail patients require a multidisciplinary care aimed at balancing between providing best possible treatment and not causing harm, exacerbating the health conditions of already fragile individuals.

Conflict of interest
None

Correspondence address
Mikołaj Młyński
Department of Cardiology and Electrotherapy
Medical University of Gdańsk
Smoluchowskiego 17, 80-214 Gdańsk, Poland
(+48 58) 584 47 60
mikolaj.mlynski@gumed.edu.pl

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