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FRAILTY CLINICAL PHENOTYPE: A PHYSICAL AND COGNITIVE POINT OF VIEW

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Abstract

Frailty is recognized as a clinical geriatric syndrome used to describe the weakest or most vulnerable older adults. Although the term frailty is commonly used in clinical practice, and the theoretical phenomenon is well accepted, it remains an evolving concept that lacks a universally accepted definition and specific diagnostic criteria. Different perspectives on frailty have led to two distinct perspectives of this phenomenon in the literature. The first describes the phenomenon based solely on physical attributes and capabilities. In contrast, more recent perspectives describe the phenomenon in broader, multidimensional terms by incorporating the concept of cognitive frailty. In support of this view, there is increasing evidence that consideration of both cognitive and physical factors can better improve the ability to predict adverse health outcomes among frail older adults over physical factors alone. The recent recognition of the importance of cognitive factors has increased the complexity of this phenomenon and difficulty in developing a consensus definition. To add to this challenge, frailty can present in different stages of severity (from mild to severe), and there appears to be a dynamic relationship between these stages. Despite these challenges, a consensus on an international definition of frailty including physical and cognitive criteria is essential in order to advance research and treatment of this condition.

Keywords

definition; frailty; physical function; cognition

INTRODUCTION

Frailty is a term frequently used by practitioners to describe the weakest or most vulnerable older adults. Frailty has been described as a state of increased vulnerability to poor

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resolution of homeostasis after a stressor event, which increases the risk of adverse health outcomes, including fall-related injuries, delirium, hospitalization, disability, and even death [1, 2]. Accordingly, frailty is associated with high utilization of health care resources, especially within the last two years of life [3]. Thus, there is great importance in identifying and treating individuals who are frail or at risk of becoming frail to maximize their functional independence for as long as possible.

It is widely accepted that the prevalence of frailty increases dramatically with age [4], and appears to be a result of a vicious cycle influenced by endogenous and exogenous factors. The United States Census Bureau has predicted that by 2050, Americans aged 65 years or older will number nearly 89 million people, which is more than double the number of older adults in the United States in 2010 [5]. Given these projections, it is critical that healthcare practitioners are able to identify individuals with this condition or at risk for this condition. Without intervention, the number of frail older adults is likely to dramatically increase in the next few decades. Thus, there is an urgent need for interventions that can assist frail older adults in maintaining independence and reducing adverse health outcomes associated with frailty.

Although the term frailty is commonly used in clinical practice, and the theoretical phenomenon is well accepted, it remains an evolving concept that lacks a consensus definition and specific diagnostic criteria [6]. Because there is no universal and accepted definition of frailty, this phenomenon can mean different things to different healthcare practitioners. Without an operational definition available in clinical practice, the health practitioner's ability to recognize and provide care for this phenomenon is limited [1, 6].

The challenge in developing a consensus definition of frailty is due in large part to the complexity of the phenomenon, which involves many different physiological, cognitive, and psychological systems. Because no single manifestation of frailty can encompass the whole of the symptoms or signs present, there is growing evidence that defining frailty in clinical practice and research remains paradoxically difficult. Different definitions have been proposed for a variety of reasons including: (1) differences in health care systems across countries, (2) debate over whether frailty is fundamentally distinct from sarcopenia or dynapenia, (3) ambiguity surrounding diagnosing a person with loss of independence, (4) novelty of the inclusion of the roles of cognitive and social function in the frailty process, and (5) variations in the tools used to assess frailty. To add even more complexity to this process, frailty presents in different stages of severity (from mild to severe) and is characterized by the dynamic relationship between these stages. Despite these challenges, a universally accepted operational definition of frailty is critical for continued clinical care, research, and health policy. As suggested by Rockwood and Hubbard (2004), frailty needs to be understood as a quantifiable entity, rather than viewed as a subjective and imprecise concept [4]. Therefore, there is an important need to come to a consensus definition of frailty.

As noted above, one of the primary reasons that there is not a universally accepted definition of frailty is that there is ongoing debate among experts over the concept of frailty itself. Past definitions of frailty have tended to focus exclusively on a physical phenotype, but more

recent definitions are broader and combine physical indicators with cognitive, functional, and psychosocial indicators of frailty [7]. For example, impairments in cognition are beginning to be considered as critical components of this condition and may lead to a more holistic approach to treatment [7, 8]. These different perspectives on frailty have led to two distinct definitions of this phenomenon in the literature. The first perspective on frailty describes the phenomenon based solely on physical capabilities. The second perspective on frailty describes the phenomenon in broader, multidimensional terms. Based on this second definition, different presentations of frailty can be encountered by the clinician, since the individual may experience impairments in one domain but not another.

Inconsistent operationalization of frailty status has resulted in widely varying prevalence estimates between studies. The prevalence of frailty is around 11%; 10% regarding physical frailty and 14% regarding the broad phenotype of frailty [7]. However, geriatric frailty has been reported in 20-30% of adults over 75 years, and its occurrence increases with advancing age [9]. Furthermore, women tend to develop the frailty syndrome more than men [7]. In the following sections, we present information on the use of the physical phenotype of frailty in clinical practice and then describe more novel cognitive approaches to defining and treating frailty.

PHYSICAL FRAILTY: FROM CONCEPT TO CLINICAL PRACTICE

The *physical frailty* syndrome has been proposed to be a clinical condition characterized by an abnormal decline in physiologic reserves that increases stress and reduces an individual's ability to maintain homeostasis and thus leads to vulnerability [2]. The differentiation between normal aging and frailty appears to be indistinct because some factors, such as the loss of muscle mass (sarcopenia) and strength (dynapenia), occur throughout the process of aging. To distinguish physical frailty from aging, the widely used domains include 'shrinking' with weight loss and sarcopenia, weakness with low grip strength, exhaustion or poor endurance, slow motor performance (e.g. slow walking speed, decreased balance), and decreased physical activity as a marker of low energy expenditure [2].

Although there is not a universally accepted operational definition of physical frailty, the most commonly used definition of a physical phenotype of frailty comes from Fried and colleagues (2001) who proposed identifying frailty by using the Fried Frailty Index [10]. The Fried Frailty Index is used to assess the presence of physical frailty if three or more symptoms are observed: (1) shrinking (i.e., a nutritional/metabolic component assessed by unintentional weight loss), (2) weakness (i.e., indicated by muscle strength), (3) poor endurance and energy (i.e., self-reported exhaustion), (4) slowness (i.e., demonstrated by slow walking speed), and (5) low amounts of physical activity [10]. Strong associations have been observed between the physical frailty phenotype, as defined by Fried *et al.*, and the risk of developing certain health related outcomes. Thus, physical frailty could be partially explained by the occurrence of age-related body composition changes loss of muscle mass, reduced muscle quality, and increased fat mass, which altogether precipitate the development of frailty syndrome in older adults.

The Fried Frailty Index has shown its clinical application by diagnosing frailty in epidemiological studies [10]. It is relatively easy to use and allows for rapid assessment of

physical frailty; however, administration of certain measurements, such as those for muscle strength and gait speed, could be difficult to implement in some clinical settings due to lack of proper equipment, time, and/or space to conduct the assessments. It is also not possible to use the Fried model for assessment in the presence of disability or cognitive impairment, which seems to affect the reliability. With the exception of objectively measured gait speed, which is a strong predictor of poor clinical outcomes in different populations [11], the added value of the other criteria used in Fried's definition is not known. Furthermore, the heterogeneous constellation of the Fried criteria includes very diverse phenotypes of frailty, making the syndrome difficult for targeting with specific pharmacologic interventions. From the interventional perspective, a more restrictive definition of frailty, involving for example, only physical performance, would be of more practical utility.

COGNITIVE FRAILTY: FROM CONCEPT TO OPERATIONAL DEFINITION

While physical frailty is a widely recognized problem in the elderly, only in recent years has the term *cognitive frailty* emerged in the literature. Although many researchers study agerelated cognitive decline and dysfunction, it is not typically conceptualized in a manner consistent with current definitions of frailty. The term cognitive frailty has been used as a general descriptor for cognitive impairment occurring as people reach advanced age, or to refer to cognitive disturbances or pre-dementia occurring in association with other medical conditions [12]. The current working definition of cognitive frailty, however, provides a foundation for clinical studies aimed at establishing an operational definition of this phenomenon.

A growing body of literature suggests a significant association between age-associated declines in both physical and cognitive function [13-15]; however, until recently, cognitive frailty lacked a working operational definition in the literature. Motivated by growing awareness that many people with physical frailty are also prone to cognitive difficulties, an international consensus group comprised of investigators from the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics recently established a working definition for cognitive frailty in older adults [16]. The consensus group summarized cognitive frailty as a heterogeneous clinical manifestation characterized by the simultaneous presence of physical frailty and cognitive impairment, in the absence of dementia [16].

The term cognitive frailty implies a parallel with physical frailty. The definition of cognitive frailty, however, is dependent on its diagnostic criteria. Unlike physical frailty, the primary criteria for cognitive frailty is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance leading to dementia. The recently proposed definition of cognitive frailty has not been empirically tested yet, and past investigators have focused on a variety of different phenomena related to the concept of cognitive frailty [17].

Several questions must be addressed in future clinical studies. How do we characterize phenotypic differences among people with cognitive frailty? A clinical dementia rating (CDR) = 0.5 is likely too narrow to capture the heterogeneity of cognitive frailty in older adults, and individuals without cognitive impairment may still be vulnerable to functional

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decline under certain conditions. This occurs commonly during hospitalization, in response to extreme stress, or to changes in the physical environment in the elderly [18]. As such, vulnerability to alterations in cognitive function under such conditions may be an essential feature of cognitive frailty. What is the relationship between cognitive frailty and cognitive reserve? Cognitive reserve refers to the capacity of a person to resist cognitive impairment or decline [17]. While cognitive reserve and cognitive frailty are likely to be associated, their relationship is not well understood. Is there value in excluding brain disorders from cognitive frailty? Excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Accordingly, there may be value in dichotomizing cognitive frailty between people with or without pre-existing brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

The current working definition of cognitive frailty provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. The construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability for cognitive functional decline among people with or without physical frailty. Though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors, growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, is independently associated with cognitive decline [13-15]. Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Prospective clinical studies are needed to assess the reliability and predictive validity of the operational measure of cognitive frailty.

REDEFINING FRAILTY: EMERGING DEFINITIONS

Based on a growing body of literature, it seems that it is no longer satisfactory to define frailty in terms of physical attributes and capabilities alone since there are other factors involved in the frailty syndrome. A limitation of the Fried model is that it does not account for the role of cognition and other psychosocial factors in determining the frailty status. There is increasing evidence that such factors need to be considered and could improve the ability to predict adverse health outcomes. Pilotto *et al.* (2012) examined the prognostic accuracy of frailty assessment inventories for mortality among hospitalized older adults and found that both cognitive and physical factors were important in predicting this outcome [19].

Numerous other definitions of frailty have added to the current controversy related to which components should be included in the frailty syndrome, in addition to physical manifestations. For example, Rockwood *et al.* (1996) conceptualized frailty as a multidimensional construct with both physical and cognitive origins [20]. Later, Panza *et al.* (2006) attempted to specify different models of frailty in pre-dementia and dementia

syndrome [21]. More recently, Rockwood and Mitnitski (2011) proposed a comprehensive definition of the frailty syndrome that is based on an "accumulation of deficits" model. For this definition, a frailty index is determined based on the total number of impairments or deficits present in the individual [22]. The frailty index is based on the accumulation of up to 70 deficits that are coded as binary variables. This frailty index predicts health outcomes, such as mortality, progression of disability, and institutionalization in different populations [23]. Since the model contains 70 assessment items, its utility in clinical practice may be limited; however, it may be useful to ascertain the effectiveness of any intervention. Yet, even this frailty index lacks the ability to discriminate across the frailty spectrum (i.e., mild, moderate, or severe). Finally, the choice of components to be included in the frailty definition continues to be a contentious issue with important implications. For example, some authors have included disability and functional decline as components of frailty [24, 25], while others regard disability and functional decline as outcomes [10, 26].

With the increasing number of older adults, research interests in gerontology are growing. An additional challenge with defining frailty is distinguishing it from related concepts from other fields of study (e.g., muscle quality vs. muscle strength vs. muscle power vs. muscle mass), particularly as they relate to physical function in older adults. For example, the European consensus definition of sarcopenia [27], which now includes criteria for gait speed and muscle strength, is close to and/or overlaps with the Fried frailty phenotype. The lack of ability to distinguish between sarcopenia and frailty could have important research and treatment implications.

CONCLUSION

Frailty is widely recognized as a specific, clinical geriatric syndrome, yet there are no universally accepted definitions or clinical screening tools for this condition. The development of a consensus operational definition of frailty is essential to advance the understanding of the causes and improve the treatment of this syndrome. Such a definition should be helpful in characterizing subsets of vulnerable older people (i.e., those with chronic disease conditions), who are not evaluated for disability risk in the clinical health care process. The following factors will contribute to advancing research and treatment of this condition: (1) a consensus on an international definition of frailty including physical and cognitive criteria; (2) the development of simple screening tools for frailty; (3) longitudinal studies of factors that predict frailty and its adverse health outcomes, and (5) translation into clinical practice of the scientific findings regarding the predictors and treatments for this condition.

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