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DIFFERENT MODELS OF FRAILTY IN PREDEMENTIA AND DEMENTIA SYNDROMES

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Abstract: Dementia is an increasingly common disease in the aging population, and the numbers are expected to rise exponentially in coming years. Therefore, there is a critical need to potentially individualize new strategies able to prevent and to slow down the progression of predementia and dementia syndromes. Despite a substantial increase in the epidemiological and clinical evidence on frailty, there is no consensus on its definition or on what criteria should be used to identify older individuals with frailty. Frailty appears to be a nonspecific state of vulnerability, which reflects multisystem physiological change. In fact, current thinking is that not only physical but also psychological, cognitive and social factors contribute to this multidimensional syndrome and need to be taken into account in its definition and treatment. Cognition has already been considered as a component of frailty, and it has been demonstrated that it is associated with adverse health outcomes. In a recent population-based study, physical frail demented patients were at higher risk of all-cause mortality over 3- and 7-year follow-up periods. Several studies have also reported that physical frailty is associated with low cognitive performance, incidence of Alzheimer's disease (AD), and mild cognitive impairment, and AD pathology in older persons with and without dementia. Most frailty instruments use a dichotomous scoring system classifying a person as either frail or not frail, while a continuous or an ordinal scoring system on multiple levels would be preferable to be used as an outcome measure. Recently, a Multidimensional Prognostic Index (MPI), derived from a standardized comprehensive geriatric assessment, was effective in predicting short- and long-term mortality risk in hospitalized patients with dementia. Overall taken together these findings supported the concept that outcome measures linked to multidimensional impairment may be extremely important in making clinical decisions, especially for monitoring drug treatment in randomized clinical trials also for predementia and dementia syndromes.

Key words: Physical frailty, frailty indexes; all-cause mortality, dementia, Alzheimer's disease, mild cognitive impairment, comprehensive geriatric assessment.

Introduction

In the next couple of decades, given the increasing aging of the population, the burden of age-related neurodegenerative diseases, particularly dementia, is expected to increase dramatically in both developed and developing nations. Dementia is a syndrome defined by impairments in memory and other cognitive functions that are severe enough to cause significantly reduced performance from a previous level of social and occupational functioning. Given the increasing impact of cognitive decline, there is a critical need to potentially individualize new strategies able to prevent and to slow down the progression of predementia and dementia syndromes (1-4). However, the deterministic boundaries of perceived normal cognitive aging are not clearly defined while the clinical categorization of predementia and dementia syndromes remain, at present, a work in progress. In western countries, the most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), with respective frequencies of 70% and 15% of all dementias (5). The 2010 figures suggested that 5.3 million Americans have AD (6), with > 26 million patients with AD worldwide, and an expected increase to more than 106 million by 2050 (7). Clinically, AD is characterized by progressive cognitive decline typically beginning with impaired memory, gradually leading to a complete psychological and physical dependency and finally to death within one to two decades. Within the term "predementia syndromes", mild cognitive impairment (MCI) is, at present, the most widely used term to indicate nondemented aged persons with no significant disability and a mild memory or cognitive impairment that cannot be explained by any recognisable medical or psychiatric condition, with a high rate of progression to dementia (8-10). Recently, a sub-classification of MCI has been proposed according to its cognitive features (including dysexecutive MCI and amnestic MCI (aMCI) or aMCI and non-amnestic MCI (naMCI); single or multiple domain aMCI or naMCI) and clinical presentation (MCI with parkinsonism or cerebrovascular disease, CVD), or likely aetiology (MCI-AD, vascular MCI, or MCI-Lewy Body Disease), and all represent an attempt to exert some control over this heterogeneity (10). The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage (11). The heterogeneous group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology has been defined recently with the

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term Vascular Cognitive Disorder (VCD) (11, 12). The main categories of VCD are Vascular Cognitive Impairment (VCI) [i.e., vascular cognitive impairment no dementia (vascular CIND), and vascular MCI], VaD, and mixed AD plus CVD, previously termed "mixed dementia" (11, 12).

Current epidemiological evidence supported the hypothesis that modifiable vascular and lifestyle-related factors are associated with the development of dementia and predementia syndromes in later life (1-4), opening new potential avenues for the prevention of these diseases. In fact, drugs currently used for the treatment of AD partially stabilize patients' symptoms without modifying disease progression, and, at present, there is no curative treatment for dementia and AD, nor there is a therapeutical approach to prevent the conversion of MCI to dementia (13, 14). In particular, among potentially modifiable risk factors, the impact of several operational definitions of frailty on cognitive decline has been the subject of recent interest (15-17). Epidemiological and clinical studies focused their attention on an increasingly important concept in both clinical care of older persons and research in aging, i.e., frailty, a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (18). However, as frailty is probably, at present, a more elusive and not pinpointed concept, how best to operationalize this syndrome is still controversial (19). This clinical syndrome is generally associated with a greater risk for adverse outcomes such as falls, disability, institutionalization, and death, in clinical criteria for physical frailty (18) or in the so called "frailty indexes" (20, 21). In particular, an emerging consensus promotes a definition of frailty on the basis of a multidimensional approach (20-23), so the evaluation of frailty employs a frailty index, which is calculated by considering a number of potential deficits. These deficits can be symptoms, signs, diseases, disabilities or abnormal laboratory values (20, 21), so developing an integral conceptual definition of frailty as a multisystem physiological change occurring in the elderly that determine an increase of risk for accelerated physical and cognitive decline, disability and death even in absence of specific diseases (20-23).

In this review article, we summarized the findings of the studies of different frailty concepts and operational definitions in relation to cognitive impairment or decline, predementia, and dementia syndromes from the English literature published before November 2010. We reviewed clinical and epidemiological studies from the international literature, including both cross-sectional and longitudinal studies that involved subjects aged 65 years and older and where description of the operational definitions of frailty and the diagnostic criteria of predementia or dementia syndromes has been attempted. Attention was also paid to the possible mechanisms behind reported associations of frailty operational definitions with cognitive impairment or decline, predementia and dementia syndromes. We searched through the PubMed database of NCBI (available at http://www.ncbi.nlm.nih.gov) by author and the following keywords: frailty, multidimensional geriatric assessment, frailty index, physical frailty, mild cognitive impairment, MCI, dementia, Alzheimer's disease, vascular dementia, and predementia syndrome.

Conceptual and operational definitions of frailty

At present, different conceptual definitions of frailty have been reported in the literature (20-23). Indeed, a first distinction must be made between conceptual and operational definitions. Ideally, a conceptual definition must give direction to the operationalization of the concept (22). However, from reviews containing conceptual definitions of frailty can be obtained very different views on frailty (24–27). Some definitions are based on physical diminution in the elderly person (15, 28, 29). Some researchers have criticized these definitions (25-27, 30), suggesting that an integral approach is needed for the concept of frailty, an approach in which the focus is not exclusively on physical problems in older people, but which also incorporates psychological and social problems, and is thus based on the integral functioning of the individual (22, 31). Based on the results of the literature search, questionnaires, and expert meetings, this integral conceptual working definition of frailty takes into account of the principles formulated earlier and combines essential components of existing conceptual definitions of frailty (22, 31). This definition indicates frailty as: "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" (22). It should be noted that physical frailty (32, 33), psychological frailty, and social frailty cannot be seen in isolation from each other; indeed, this conceptualization of frailty is based on a holistic view of the person (22, 23).

Frailty phenotype and cognitive decline

The "phenotypic" definition of frailty (34, 35) was proposed by Fried and colleagues first working with the Cardiovascular Health Survey (CHS) (15). By convention, the CHS definition of physical frailty proposes five items: weight loss, exhaustion, weakness, slow walking speed, and low levels of physical activity. A person is said to be frail when three or more are present, "pre-frail" when they exhibit only one or two of these characteristics, and "robust" when they have none (15). Estimates using the CHS operational definition of physical frailty have been widely reproduced, and aspects of the definition have been cross-validated in a number of ways (36). However, while other population-based studies confirmed original findings from the CHS of the overlaps and dissociations between frailty, disability and comorbidity, there were important differences in the reported prevalence estimates (from 6.9% to 20.0%) (15, 36-44). Very recently, in the Italian

Longitudinal Study on Aging (ILSA), evaluating 2,581 individuals from a population-based sample of 5,632 subjects aged 65-84 years, a phenotype of physical frailty was operationalized slightly modifying the CHS criteria (30), and was identified by the presence of three or more frailty components. In the ILSA, a prevalence rate of 7.6% (95% confidence interval (CI) 6.55-8.57) for physical frailty in a community-defined cohort of 65-84 year old subjects was found (45).

In previous studies, cognition has already been considered as a component of frailty (18), and it has been demonstrated that it is associated with adverse health outcomes (16, 17). In the ILSA, both lower cognition and greater depressive symptoms were associated with physical frailty (45). At present, the ILSA is the first population-based study in which physical frailty has been investigated as possible determinant of short and long-term all-cause mortality in demented subjects. The effect of frailty on disability was estimated in presence of the competing risk of death from any causes. In particular, frail demented subjects were 17.8%, frail individuals without disability were 39.3%, and without comorbidity were 9.1%. Frailty was associated with a significantly increased risk of all-cause mortality in 3- and 7-year follow-up periods, but with significant increased risk of disability only in a 3-year follow-up. Frail demented patients were at higher risk of all-cause mortality over 3- and 7-year follow-up periods, but not of disability (45) (Table 1).

Therefore, in the ILSA, physically frail demented patients, after adjustment for possible confounders at baseline, were at higher risk of all-cause mortality but not of disability in short- and long-term periods (45). However, some of the physical frailty components have been associated with survival in demented subjects. In fact, long-term survivors among demented subjects had delayed emergence of motor symptoms (46), while unintentional weight loss was predictive of decreased survival in dementia (47). Physical activity can reduce the risk of cognitive decline and dementia (48), but clinical trial evidence for the effectiveness of physical activity programs in managing or improving cognition, function, behavior, depression, and mortality in people with dementia is still insufficient overall (49). Furthermore, very recent findings from the Three-City Study suggested that cognitive impairment improved the predictive validity of the operational definition of physical frailty, increasing the risk to develop disability. On the contrary, risk of death also tended to be higher in cognitively impaired frail participants than in their nonfrail counterparts without cognitive impairment, even if the results were not statistically significant (18). Although the promising findings from the ILSA (45), further investigations are needed in larger samples of elderly subjects with longer follow-up to determine the role of physical frailty in survival in demented subjects also in relation to other environmental and genetic factors.

Recently, beyond the possible role of physical frailty in predicting survival in dementia, several studies have also reported that physical frailty is associated with low cognitive performance (50, 51), incidence of AD (52), and MCI (53), and AD pathology in older persons with and without dementia (54) (Table 1). In particular, previous cross-sectional studies reported that physical frailty was associated with the level of cognition and dementia (15, 18, 55). In the unadjusted model of the Three City Study, being frail at baseline led to twice the cumulative risk of dementia at 4 years, although after adjusting for socio-demographic and health covariates frailty status did not remain a statistically significant predictor of dementia (18). Two longitudinal population-based studies indicated frailty syndrome as a predictor of cognitive impairment in a 10-year follow-up (55), and that it was associated with the rate of cognitive decline in a 3-year period (52). The Rush Memory and Aging Project also found that physical frailty increased the risk for MCI (53), although there is still controversy as to whether cognitive impairment may be a symptom of frailty or whether MCI is a separate syndrome, or indeed, a sign of early dementia (53, 54). Recent findings from the Rush Memory and Aging Project raised the possibility that AD pathology may contribute to frailty or that frailty and AD pathology share a common pathogenesis (54). In fact, physical frailty proximate to death was related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or Lewy body disease. This association was similar in persons with and without dementia and was unchanged even after considering level of physical activity, various physical performance measures, and chronic diseases (54). One longitudinal population-based study has examined the association of frailty or change in frailty with incident AD (52). In fact, other findings from the Rush Memory and Aging Project on 820 subjects during a 3-year follow-up showed that the risk of developing AD was 2.5 times higher when physical frailty was present at baseline (52). On the other hand, very recently, also a low Mini Mental State Examination (MMSE) score (56), a tool evaluating cognitive function, was independently associated with increased risk of physical frailty over a 10-year period in older Mexican Americans, suggesting that cognitive status may also be an early marker for future risk of physical frailty (57) (Table 1). Furthermore, several of the individual components used to construct the measure of physical frailty in these studies, including altered gait, slowed movement, weight loss, and muscle weakness have been associated with the development of dementia and incident AD (58-61). In particular, a relationship between grip strength and risk of AD was found (60), and also increased muscle strength was associated with a decrease in the risk of incident AD, of incident MCI, and with a slower rate of decline in global cognitive function during a mean follow-up of 3.6 years (61). Finally, a recent study provided preliminary empirical support for the existence of subdimensions of physical frailty within the CHS model (15). In particular, two subdimensions were identified, and cognitive impairment was part of a frailty subdimension including slower gait, weaker grip, and lower

Table 1
Principal studies on the association of different operational definitions frailty or frailty instruments with different cognitive outcomes

Reference	Study design and sample	Frailty and cognitive assessment	Principal results
Gill et al., 1996	Population-based, longitudinal study; 945 respondents from the Project Safety cohort, aged 72 years and older	A composite measure of physical performance, ADL, and MMSE	The risk of dependence increased with worsening performance, on both objective measures of physical skills and standardized assessment of cognitive status. Impairments in physical performance and cognitive status were shown to contribute independently to the risk of functional dependence, even after controlling for potential confounders
Strawbridge et al., 1998	Population-based, longitudinal study; 574 Alameda County Study respondents, aged 65-102 years	1994 Frailty Measure with four items assessing cognitive functioning	Frail persons reported reduced activities, poorer cognitive function, and lower life satisfaction. Cumulative predictors over the previous three decades included heavy drinking, cigarette smoking, physical inactivity, depression, social isolation, fair or poor perceived health, prevalence of chronic symptoms, and prevalence of chronic conditions
Fried et al., 2001	Population-based, longitudinal study; 5,745 older individuals from the CHS, aged 65 years and older	CHS frailty phenotype and MMSE	Lower cognition was associated with the frailty physical phenotype (despite exclusion of those with MMSE < 18)
Rockwood et al., 2004	Population-based, longitudinal study; 9,008 older individuals from the CSHA aged 65 years and older	The operational and rules-based definition of frailty of the CSHA was based on the GSS, a scale combining aspects of cognitive and functional performance to describe various degrees of frailty; cognitive functions were also measured with the 3MS	Among those participants described as mildly frail, 71.3% had functional impairment alone, 14.4% had cognitive impairment alone, and 14.3% had both. For those who were moderately or severely frail, coincident functional and cognitive impairments were more common, occurring in 28.1%
Rockwood et al., 2005	Population-based, longitudinal study; 2,305 older individuals from the CSHA aged 65 years and older	CSHA Clinical Frailty Scale and 3MS	Participants with higher scores on the CSHA Clinical Frailty Scale were more likely to be cognitively than those with lower scores. This frailty instrument performed better than measures of cognition, function or comorbidity in assessing risk for death
Rockwood et al., 2007	Population-based, longitudinal study; 728 institutionalized older adults in the second clinical examination cohort of the CSHA aged 65 years and older	CSHA Frailty Index, CSHA Clinical Frailty Scale, CHS phenotype, and 3MS	All three frailty measures were significantly associated with an increased risk of mortality, disability and cognitive decline, measured with the modified 3MS. When pairs of frailty measures were included in the models, only the CSHA Frailty Index was associated with a higher risk of mortality and decline in the 3MS
Buchman et al., 2007	Population-based, longitudinal study; 823 older persons (mean age: 80.4 years) without dementia who participated in the Rush Memory and Aging Project	Physical frailty phenotype operalizionated slightly modifying the CHS criteriaand based on four frailty components. Diagnoses of AD and DLB were made according to the NINCDS-ADRDA and the Report of the Consortium on DLB International Workshop. The MMSE was used to other 19 neuropsychological tests were used to create a composite measure of global cognitive function. The CIM was used for diagnostic classification purposes only	Both baseline level of frailty and annual rate of change in frailty were associated with an increased risk of incident AD. Furthermore, the level of frailty and rate of change in frailty were also associated with the rate of cognitive decline
Buchman et al., 2008	Population-based, longitudinal study; brain autopsies from 165 deceased participants from the Rush Memory and Aging Project	Physical frailty phenotype operalizionated slightly modifying the CHS criteriaand based on four frailty components. Diagnoses of AD and DLB were made according to the NINCDS-ADRDA and the Report of the Consortium on DLB International Workshop criteria. Neuropathological measures of AD pathology, Lewy bodies, and cerebral infarcts were also obtained	Physical frailty proximate to death was related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or LBD. This association was similar in persons with and without dementia.
Samper-Ternent et al., 2008	Population-based, longitudinal study; 1,370 non-institutionalized Mexican American men and women aged 65 and older from the H-EPESE with a MMSE ≥ 21 at baseline	Physical frailty phenotype operalizionated slightly modifying the CHS criteria based on five frailty components and MMSE	A statistically significant association between frailty and subsequent decline in cognitive function over a 10-year period was found in older Mexican Americans
Sarkisian et al., 2008	Population-based, longitudinal study; 1,118 high-functioning subjects aged 70-79 years from the MacArthur Study of Successful Aging	Physical frailty phenotype operalizionated slightly modifying the CHS criteria. Cognitive function was assessed using reliable tests of language, executive function, spatial ability, and verbal and nonverbal memory	Two subdimensions of were identified, and cognitive impairment was part of a frailty subdimension including slower gait, weaker grip, and lower physical activity, further increasing evidence that physical performance tests are sensitive indicators of cognitive impairment, and further supporting the hypothesis that cognitive impairment may be intrinsic to frailty

Pilotto et al., 2009	Hospital-based, longitudinal study; 262 patients aged 65 years and older with a diagnosis of dementia	The CGA-based MPI and diagnosis of dementia according to the DSM-IV, NINCDS-ADRDA, and NINDS-AIREN criteria	The MPI accurately stratified hospitalized elderly patients with dementia into groups at varying risk of short- and long-term all-cause mortality
Avila-Funes et al., 2009	Population-based, longitudinal study; 6,030 older individuals aged 65-85 years from the Three-City Study	Physical frailty phenotype operalizionated slightly modifying the CHS criteria, MMSE, and IST. Diagnosis of dementia according to the DSM-IV criteria	Frail individuals with cognitive impairment have a higher risk of IADL and ADL disability and of incident hospitalization and dementia than subjects with none of these conditions, even after adjusting for potentially confounding variables
Boyle et al., 2010	Population-based, longitudinal study; 761 older persons (mean age: 79 years) without cognitive impairment at baseline who participated in the Rush Memory and Aging Project	Physical frailty phenotype operalizionated slightly modifying the CHS criteriaand based on four frailty components. Diagnoses of AD and MCI were made according to the NINCDS-ADRDA criteria and CSHA clinical criteria. The MMSE was used to describe the cohort, while scores on other 19 neuropsychological tests were used to create a composite measure of global cognitive function. The CIM was used for diagnostic classification purposes only	No difference in the distribution of APOE genotypes was found between AD patients with and without NPS. In AD patients APOE ε4-carriers, there was an increased risk of affective and apathetic syndromes
Sourial et al., 2010	Three population-based, longitudinal studies; 839 individuals aged 75 years and older from the MUNS, 1,600 individuals aged 65 years and older from the CSHA, and 1,164 individuals aged 65 years and older from the SIPA strength, energy, cognition, and mood	Seven domains of frailty were evaluated: nutrition, physical activity, mobility,	In two of these population-based studies (CSHA and MUNS) presence of deficits for all domains separated from absence of deficits. In the SIPA, there was separation in all domains except cognition
Raji et al., 2010	Population-based, longitudinal study; 942 non-frail Mexican American men and women aged 65 and older from the H-EPESE	Physical frailty phenotype operalizionated slightly modifying the CHS criteria based on four frailty components and MMSE	Non-frail older Mexican Americans with low cognitive scores were significantly more likely to acquire one or more components of frailty over 10 years than those with higher cognitive scores
Solfrizzi et al., 2011	Population-based, longitudinal study; 2,581 individuals from the ILSA sample of 5,632 subjects aged 65-84 years	Physical frailty phenotype operalizionated slightly modifying the CHS criteria and diagnosis of dementia according to the DSM-III-R, NINCDS-ADRDA, and ICD-10 criteria	Lower cognition was associated with physical frailty. Frail demented patients were at higher risk of all-cause mortality over 3- and 5-year follow-up periods, but not of disability

ADL = activities of daily living; MMSE = Mini Mental State Examination; CSH = Cardiovascular Health Study; CSHA = Canadian Study of Health and Aging; GSS = Geriatric Status Scale; 3MS = modified Mini Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; AD = Alzheimer's disease; CIM = Complex Ideational Material; DLB = dementia with Lewy bodies; H-EPESE = Hispanic Established Population for the Epidemiological Study of the Elderly; IST = Isaac Set Test; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders-IV; IADL = instrumental activities of daily living; CGA = Comprehensive Geriatric Assessment; MPI = Multidimensional Prognostic Index; NINDS-AIREN = National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; MCI = mild cognitive impairment; MUNS = Montreal Unmet Needs Study; SIPA = French acronym of the System of Integrated Services for Older Persons study; ILSA = Italian Longitudinal Study on Aging; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders-III revised; ICD-10 = International Statistical Classification of Diseases and Related Health Problems,10th revision

physical activity, further increasing evidence that physical performance tests are sensitive indicators of cognitive impairment, and further supporting the hypothesis that cognitive impairment may be intrinsic to frailty (62). In fact, although some have referred to the CHS model of frailty as the "biological" model of frailty (in contrast to other models that include social and psychological criteria) (20-23), these findings call this into question, because several variables in the CHS phenotype of frailty appear to be integrally related to cognitive impairment (62).

These findings suggested that factors associated with the development of frailty and its components were also associated with the development of dementia and AD. For example, risk factors for cardiovascular disease (e.g., diabetes) and common vascular diseases (e.g., congestive heart failure, brain infarcts) have been related to both frailty (63) and AD (1-4). In fact, several studies showed that comorbidities like congestive heart failure, myocardial infarction, peripheral vascular diseases, diabetes, and hypertension increase the risk for frailty (63). The association between frailty and increased risk of incident AD may be linked to an underlying increased risk of stroke and cerebrovascular disease. In particular, in older patients after myocardial infarction within six months of discharge, frailty status was an independent predictors of ischemic stroke (64). Furthermore, in a cohort of acute hospital inpatients aged 70 years with atrial fibrillation, compared to the non-frail participants, the frail participants had significantly higher rates of stroke and death (65). Moreover, as seen above, physical frailty proximate to death was related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or Lewy body disease (54), although this postmortem assessment did not directly assess motor brain regions and thus might underestimate the association of frailty with cerebral infarcts or Lewy body pathology. However, frailty, dementia, and AD are complex concepts and it is likely that many other factors are also involved. In fact, beyond the

possible role of vascular risk factors and vascular-related diseases, there are several potential pathways by which frailty could contribute to cognitive decline, although, at present, the mechanisms underlying this suggested association remained unclear. One of these underlying pathogenetic factors may be inflammation. Increased markers of inflammation such as C-reactive protein (CRP) or proinflammatory interleukins (IL) are common and have been implicated in frailty (66), cognitive impairment (67), and dementia (68). In fact, in the above-mentioned study on the possible subdimensions of the CHS model of physical frailty, in the expanded model, one of the subdimensions identified with elevated predictive validity for mortality included higher IL-6 and CRP (62). In some forms of dementia, particularly AD, primary and supplementary motor cortices, the substantia nigra and the striatum are often altered (69). Studies have shown that alterations in these areas of the brain are associated with modifications in the components of frailty such as weight loss and slow gait (70, 71), suggesting the possibility that changes in neural systems that control motor function, metabolism, and fatigue may be present in frailty. Some other, less well-studied but potential mechanisms may include decreased energy production or metabolic issues and stress. These different mechanisms are not mutually exclusive and underscore the need for further studies to further explicate the biological basis of the association between physical frailty and cognitive impairment in old age.

Multidimensional models of frailty in dementia and predementia syndromes

As above reported, in recent years, frailty is acknowledged to be not only a biological or physiological state, but also a multidimensional concept (20, 21, 35, 72). The multidimensional nature of the concept of frailty demands a multidisciplinary approach. Indeed, results of evidence-based research suggest that integrated housing, welfare, and care interventions for frail older people have a major impact on aspects such as health, quality of life, satisfaction, pattern of health care utilization, and costs (73).

A very recent systematic review evaluated clinimetric properties and searched for the best available frailty instrument that can be used as an evaluative outcome measure in clinical practice and that may be useful in observational and experimental studies (21). Based on recent studies (22, 23, 74-76), a list of eight frailty risk factors that are mentioned to be of great importance to the concept of frailty were identified (21), including in the physical dimension: nutritional status, physical activity, mobility, strength and energy, in the psychological dimension: cognition and mood, and in the social dimension: lack of social contacts and social support (25). On this basis, at least twenty frailty instruments have been described (21), and cognition was present in only 40% of them (31, 51, 77, 78, 80, 81-87). All these frailty instruments are multidimensional in nature, and mostly based on a standardized Comprehensive Geriatric Assessment (CGA) (81, 82, 85, 86, 88, 89). However, the overall results of the assessment by using these frailty instruments, suggested that they are mainly developed and validated as risk assessment tools, and not as possible outcome measures (21).

Only a few studies made a comparison between frailty instruments (80, 86, 90-93), concluding that different instruments may identify older people at risk of adverse health outcome (86, 90), but they may capture different sub-populations (80, 92, 93). In particular, in older individuals institutionalized in nursing homes, comparing the CHS physical definition of frailty (15), the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (17), and the Frailty Index (77-80), while all these frailty measures were significantly associated with an increased risk of mortality, disability and cognitive decline, measured with the modified MMSE (3MS) (94), when pairs of frailty measures were included in the models, only the Frailty Index was associated with a higher risk of mortality and decline in the 3MS (91) (Table 1). Finally, a recent report examined the relationships among seven frailty domains (nutrition, physical activity, mobility, strength, energy, cognition, and mood), using data from three population-based studies, the Montreal Unmet Needs Study (MUNS), the CSHA, and the System of Integrated Services for Older Persons study (French acronym, SIPA) (23). In two of these studies (CSHA and MUNS) presence of deficits for all domains separated from absence of deficits. In the SIPA, there was separation in all domains except cognition. All these data suggest that frailty is a multidimensional concept for which the relationships among domains differ according to the population characteristics. These domains, with the possible exception of cognition, appeared to aggregate together and share a common underlying construct (23). Alternatively, it may be that frailty involves specific aspects of cognition not measured in the three studies, such as executive function or psychomotor speed (33, 63, 95), rather than overall impairment (Table 1).

Unfortunately only very few studies explored the multidimensional impairment as a frailty concept in hospitalized older patients. Recently, a Multidimensional Prognostic Index (MPI) for 1-year all-cause mortality, entirely derived from a standardized CGA, was developed and validated in two independent cohorts of older hospitalized patients for acute diseases or relapse of chronic diseases (96-101). A typical assessment schedule of CGA includes the administration to the older subject a number of evaluation instruments that focus on relevant clinical and functional areas to establish individual impairments or risk factors that may improve with specific interventions. Widely diffuse in the geriatric practice, the instruments on which also the MPI was based (96), proved to be clinically useful for evaluating functional disabilities in the Activities of Daily Living (ADL) (102) and the Instrumental Activities of Daily Living (IADL) (103), the cognitive status for dementia screening [MMSE (56) or the Short-Portable Mental Status Questionnaire (SPMSQ) (104)], the risk or the presence of depression [Geriatric Depression Scale (GDS) (105)], the nutritional status [Mini-Nutritional Assessment

(MNA) (106)] or the risk of pressure sores in patients at high risk of immobilization or bed-ridden [Exton-Smith scale (ESS) (107)]. Moreover, the CGA includes a careful evaluation of comorbidities by Comorbidity Illness Rating Scale (CIRS) (108), or other tools (109), as well as of medication use for the evaluation of the appropriateness of prescriptions (110), and the risk for adverse drug reactions (111). In particular, the MPI was calculated by aggregating data from six specific questionnaires, i.e., ADL, IADL, SPMSQ, CIRS-CI, MNA, EES as well as data on number of medications and cohabitation status, for a total of eight domains (96). For each domain a tripartite hierarchy was used, i.e., 0 = no problems, 0.5 = minor problems, and 1 = major problems, based on conventional cut-off points derived from the literature for the SPMSQ, MNA, ESS and ADL/IADL or by observing the frequency distribution of the patients at various levels to identify points of separation for comorbidities and number of medications. The sum of the calculated score from the eight domains was divided by 8 to obtain a final MPI score between 0 and 1. For analytical purposes, MPI was expressed as low (MPI-1 value < 0.33), moderate (MPI-2 value between 0.34 and 0.66) and severe risk (MPI-3 > 0.66) of all-cause mortality. Further details on mathematical methods used to identify the best MPI cut-off points have been previously reported elsewhere (96).

Among chronic diseases, the MPI accurately stratified into groups at varying risk of short- and long-term all-cause mortality, hospitalized older patients with both upper gastrointestinal bleeding and liver cirrhosis (97, 98), community-acquired pneumonia (99), congestive heart failure (100), and dementia (101). In particular, the MPI was effective in predicting short- and long-term mortality risk in elderly subjects with dementia admitted to a geriatric hospital ward (101) (Table 1), and given that in patients with dementia, clinical outcome and mortality result from a combination of psychological, biological, functional and environmental factors, tools that effectively identify patients with different life expectancy should be multidimensional in nature (89). Previous epidemiological studies suggested that age, male sex, socio-demographic characteristics, the severity of dementia, other comorbid conditions, disability, and genetic characteristics may be significant predictors of mortality in the elderly population with dementia (112, 113). Overall taken together these findings supported the concept that considering multidimensional aggregate information and frailty syndrome could be very important for predicting short- and long-term all-cause mortality in older subjects with dementia, and that it may be important for the identification of the more adequate management of these patients.

Conclusions

Over the past twenty-five years, frailty appeared to be one of the greatest challenges for health care professionals, and numerous models and approaches for its study have been advocated. Although there is no clear consensus on its definition or on what criteria should be used to identify older individuals with frailty, an emerging consensus promotes a definition of frailty on the basis of a multidimensional approach. In fact, the causes of frailty are complex and must be accepted as multidimensional based on the interplay of genetic, biological, physical, psychological, social and environmental factors. In this regards, the inclusion of other common age-related conditions, potentially linked to frailty, is a topic of considerable debate. Of these age-related conditions, cognition has already been considered as a component of frailty. In a recent population-based study, physical frail demented patients were at higher risk of all-cause mortality over 3- and 7-year follow-up periods. Several studies have also reported that physical frailty is associated with low cognitive performance, incidence of AD, and MCI, and AD pathology in older persons with and without dementia. Numerous ways to measure frailty have been described in literature, i.e., self-report questionnaires or interviews, performance tests and combinations of both. Frailty instruments, however, are often developed and validated as prognostic instruments, and the clinimetric properties of these instruments as evaluative outcome measures are unclear. Most frailty instruments use a dichotomous scoring system classifying a person as either frail or not frail, while a continuous or an ordinal scoring system on multiple levels would be preferable to be used as an outcome measure to better capture the dynamic and multidimensional nature of frailty. Therefore, possible outcome measures linked to multidimensional impairment may be extremely important in making clinical decisions, especially for monitoring drug treatment in randomized clinical trials (RCTs) also for predementia and dementia syndromes. Furthermore, the evaluation of cognitively impaired older patients with a multidimensional frailty instrument may be useful in identifying possible links among various frailty domains and cognitive impairment, opening new viable routes for the prevention of dementia.

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