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A multidimensional approach to frailty in older people

Alberto Pilotto[a,b,*], **Carlo Custodero**[a], **Stefania Maggi**[c], **Maria Cristina Polidori**[d], **Nicola Veronese**[b,e], **Luigi Ferrucci**[f]

[a]Department of Interdisciplinary Medicine, University of Bari Aldo Moro, Bari, Italy

[b]Geriatrics Unit, Department of Geriatric Care, Orthogeriatrics and Rehabilitation, E.O. Ospedali Galliera, Genova, Italy

[c]National Research Council (CNR), Aging Section, Padova, Italy

[d]Ageing Clinical Research, University Hospital of Cologne, Germany

[e]Azienda ULSS 3 Serenissima, Primary Care Department, District 3, Venice, Italy

[f]National Institute on Aging, NIH, Baltimore, MD, United States

Abstract

Frailty is an important factor determining a higher risk of adverse health outcomes in older adults. Although scientific community in the last two decades put a lot of effort for its definition, to date no consensus was reached on its assessment. The mainstream thinking describes frailty as a loss of physical functions or as accumulation of multiple deficits. Recently, a novel conceptual model of frailty has emerged based on the loss of harmonic interaction between multiple domains (also referred as dimensions) including genetic, biological, functional, cognitive, psychological and socio-economic domain that ultimately lead to homeostatic instability. Therefore, the multidimensional aspects of frailty condition could be captured by the comprehensive geriatric assessment (CGA) and its derived Multidimensional Prognostic Index (MPI). This instrument has been applied in different clinical settings and in several cohorts of older adults with specific acute and chronic diseases, showing always excellent accuracy in stratifying population according the mortality risk and other negative health outcomes, i.e. hospitalization, institutionalization or admission to homecare services. This MPI "plasticity" provides a single numerical prognostic index which could be helpful in clinical decision making for the management of frail older adults.

Keywords

Comprehensive geriatric assessment; Multidimensional prognostic index; Frailty

*Corresponding author at: Department Geriatric Care, Orthogeriatrics and Rehabilitation, E.O. Ospedali Galliera, Via Mura delle Cappuccine 16, 35121, Genova, Italy. alberto.pilotto@galliera.it (A. Pilotto).

Declaration of Competing Interest

None to declare.

1. Introduction

Frailty is a common condition in older people. Among models traditionally used in geriatric medicine to define this condition, the multidimensional model can be considered as a novel approach to frailty characterized by the loss of harmonic interaction between multiple domains/dimensions (including genetic, biological, functional, cognitive, psychological and socio-economic domain) that ultimately lead to homeostatic instability. Therefore, the multidimensional aspects of frailty condition could be captured by the comprehensive geriatric assessment (CGA) and its derived Multidimensional Prognostic Index (MPI).

In this viewpoint article, we aim to summarize the current state of the art, the applications and the future directions of applicability of the CGA-based MPI for measuring frailty in older people.

2. Frailty

Frailty is a condition characterized by a decline in functioning across multiple physiological systems, accompanied by an elevated vulnerability to stressors (Hoogendijk et al., 2019). Frailty occurs with ageing and carries a high risk of multiple adverse health outcomes, which ultimately causes hospitalization, falls, institutionalization, and death (Clegg et al., 2013; Hoogendijk et al., 2019).

Frailty is a prevalent condition among older adults, with an estimated prevalence of 10 % in community-dwellers (Collard et al., 2012), but higher in other settings such as hospital where the frailty prevalence may range from 18 % to 40 % of patients (Cunha et al., 2019).

Recent literature has also reported that frailty is associated with a higher risk of cardiovascular disease (Veronese et al., 2017a), depression (Soysal et al., 2017) and finally to a reduction in quality of life (Kojima et al., 2016) and an important economic burden (Hajek et al., 2017).

Moreover, research suggests that frailty is caused by an overt age-associated dysregulation of multiple homeostatic systems that causes progressive loss of physiological reserves that is so severe that results in a multifunctional impairment and eventually in pathology and death (Fontana et al., 2013).

3. Underlying mechanisms of frailty

The aging process is modulated by the neuro-immuno-endocrine system, nutritional status and physical activity. These regulatory mechanisms become less effective in frail older persons, at least in part because of the presence of low-grade inflammation, i.e. inflammageing, and excessive and unopposed oxidative stress. Probably other common mechanisms are shared with the aging process, age-related diseases and geriatric syndromes including frailty (Franceschi et al., 2018). Over the long term, the accumulation of unrepaired damage at both somatic and stem cells may lead to a loss of their metabolic and functional activities, including the age-associated decline in immune function, i.e. immunosenescence. Indeed, inflammageing and immunosenescence have been suggested as

contributors to frailty and sarcopenia (Wilson et al., 2017), i.e. the progressive loss of skeletal muscle mass and strength associated to reduced physical performances, conditions that are generally considered characteristic components of physical frailty (Cruz-Jentoft et al., 2019). Of note, similar mechanisms probably explain the effect of frailty of cardiovascular, respiratory, renal, hemopoietic and metabolic systems (Ferrucci and Fabbri, 2018; Franceschi et al., 2018). Hence, not surprisingly, poor nutritional status, may sustain directly and/or indirectly the downward cascade typical of frailty or, vice-versa, most of the interventions that reverse or slow down frailty are based, at least in part, on improving nutrition (Calder et al., 2017; Custodero et al., 2018) (Fig. 1).

4. Frailty models

Over the last two decades, several methods have been proposed to assess frailty condition which underlie different conceptual models of frailty. The phenotypic model identifies frailty by the presence of more than two of five features: a) unintentional weight loss; b) exhaustion; c) low physical activity level; d) slow walking speed; e) muscle weakness (Fried et al., 2001). The multiple-deficits model rates frailty by the number of functional, sensory and clinical deficits (Rockwood and Mitnitski, 2007). These two models and relative measurement tools, catch different trajectories of frailty in older persons and, not surprisingly, studies based on the two different definitions produced quite different results (Collard et al., 2012). For this reason, it has been suggested that in spite of the evidence that these tools convey important information on response to treatments and risk of adverse health outcomes, the translation of this evidence into clinical practice is still limited (Clegg et al., 2013; Dent et al., 2016). We argue that in both cases, these tools have limited applicability to clinical practice.

5. Clinical approach to frailty: the “multidimensional” model

Recently, a novel, general conceptual model of frailty has emerged based on a hierarchical organization of three different levels of complexity, organized like the overlapping layers of an onion (Table 1) (Ferrucci et al., 2017). The inner dimension refers to biological mechanisms involved in frailty at the subcellular level (e.g. mitochondrial dysfunction, oxidative stress, DNA damage, shortening of telomere length, maladaptive DNA methylation). The intermediate layer refers to potential physiopathological mechanisms leading to frailty condition, including chronic low-grade inflammation, energetic imbalance, anabolic deficiency, neurodegeneration. The external dimension encompasses the clinical consequences and the manifestations of frailty: functional deficits, reduced mobility, cognitive impairment, loss of independence in the activities of daily living, multiple chronic diseases, polypharmacy, and geriatric syndromes. Frailty is conceptualized as the loss of harmonic interaction between domains (also referred as dimensions) including genetic, biological, functional, cognitive, psychological and socio-economic domain. In this model, multimorbidity and polypharmacy, typically encountered in older patients, are considered both as causes and effects. Regardless of the specific tool, the diagnosis of frailty could be approximated by collecting information on physical performance, mobility, cognitive and nutritional status (Rodriguez-Manas et al., 2013). The evaluation of contribution of different illnesses, in particular chronic disease, on general health status is another important aspect of

frailty (Rodriguez-Manas et al., 2013). In this exception, the condition of frailty could be captured by the traditional comprehensive geriatric assessment (CGA) that have already been introduced in geriatric clinic (Fig. 2).

6. Frailty diagnosis: the comprehensive geriatric assessment (CGA)

A systematic revision of the literature on frailty tools showed that they have excellent sensitivity, but very low specificity, limiting therefore their reliability in current clinical use for the identification and diagnosis of frailty (Clegg et al., 2015). Indeed, principal international guidelines from geriatric scientific societies discourage the use of “short” instruments as tools in community-based setting, but rather recommend an approach centered on CGA (Turner et al., 2014).

According to the multidimensional model, the identification of frailty could be approximated by CGA especially if a tool that conveys information on biological, functional, psychological, clinical, social dimensions is used (Clegg et al., 2013). Operatively, CGA is administered to the patient using specific scales that explore functional disability, cognition, depression, nutritional status, comorbidities, number of drugs used by patient, falls and pressure sores risk, cohabitation status, and social and welfare context. Growing evidence from meta-analyses and systematic reviews of randomized controlled studies carried out in different clinical settings and several specific diseases, showed that routine application of CGA significantly reduce mortality. Moreover, CGA has a positive influence on other outcomes such as institutionalization, hospitalization, and functional and cognitive status of older patients. The CGA help ensure good appropriateness of prescribing and intervention in frail older adults (Pilotto et al., 2017).

Taken together, these data suggest that CGA could be used for the identification of frailty in clinical practice. Noteworthy, a recent reflection paper on physical frailty by the European Medicines Agency (EMA) reported that a complete evaluation of frailty to support its management requires a multidimensional interdisciplinary CGA (European Medicines Agency. Committee for Medicinal Products for Human Use, 2018). In this context, the Multidimensional Prognostic Index (MPI), is recognized as a CGA-based predictive tool, able to extract information from a standard CGA to categorize frailty in three subgroups with excellent prognostic value for the identification of frailty (European Medicines Agency. Committee for Medicinal Products for Human Use, 2018).

7. The Multidimensional Prognostic Index (MPI)

The Multidimensional Prognostic Index (MPI) is a common tool for evaluating frailty, particularly in primary care and hospital settings (Dent et al., 2019). The MPI was initially developed and validated as a prognostic index predicting mortality in hospitalized older patients (Pilotto et al., 2008). MPI is a product of the CGA, that uses a mathematic algorithm including information about eight domains: functional status as assessed by basal and instrumental Activities of Daily Living, cognitive status as assessed by the Short Portable Mental Status Questionnaire (SPMSQ), nutritional status as assessed by the Mini Nutritional Assessment (MNA), mobility and risk of pressure sore evaluated by the Exton-

Smith score (ESS), multi-morbidity according to the Cumulative Illness Rating Scale (CIRS), the number of drugs to assess polypharmacy and co-habitation status (Pilotto et al., 2008). Interestingly, the domains included in the MPI are assessed by means of already aggregated and multidimensional in nature tools (i.e. ADL, IADL, SPMSQ, MNA, ESS, CIRS) validated in older people and widely diffuse in clinical practice. For each domain, a tripartite hierarchy was used (0 = no problems; 0.5 = minor problems; 1 = major problems), based on conventional cut-off points derived from the literature for the singular tests. In this sense, we can say that MPI is able to translate the clinical evaluation of CGA in a score, between 0 and 1, that can accurately predict mortality and other negative outcomes and so be used as prognostic tool in older people. Then, the sum of the calculated scores from the eight domains was divided by 8 to obtain a final MPI risk score ranging from 0 = no risk to 1 = higher risk of mortality (Pilotto et al., 2008). Usually, the MPI was expressed as three grades of risk: MPI-1 low risk (MPI value ≤ 0.33), MPI-2 moderate risk (MPI value between 0.34 and 0.66) and MPI-3 high risk (MPI value > 0.66). MPI requires between 15–25 min for its complete execution and the results can be automatically obtained through the program Calculate-MPI that it is possible to download for free by the www.mpiage.eu website.

A modified short-form MPI, showed similar degree of accuracy as the original MPI, but could be completed in around 20 min (Sancarlo et al., 2011). Another MPI version, the MPI-SVaMA, has been developed and validated in community-dwelling older adults who underwent a standard CGA for being admitted to nursing home and/or homecare services in Italy (Pilotto et al., 2013). The effectiveness of MPI has been tested also in population-based studies. In a large cohort of elderly subjects living in Sweden and followed-up for over 10 years, higher MPI values predicted lower survival and more days in hospital (Angleman et al., 2015). Finally, in the context of the international project called EFFICHRONIC, it has been created and validate a self-administered version of the MPI (SELFY_MPI) proposed as screening tool for community-dwelling population (Pilotto et al., 2019a). Therefore, the MPI “plasticity” allows its application on scales derived from different clinical settings and may provide a single numerical prognostic index exploring multiple dimensions that overlap with frailty of the older subject (Table 2).

This instrument has been applied in several cohorts of older adults with specific acute and chronic diseases, showing always excellent calibration, reproducibility and accuracy in stratifying population according the risk of short and long-term mortality (Dent et al., 2016; Yourman et al., 2012).

Evidence derived from many multicenter studies demonstrated that MPI is (Table 2): 1) significantly more accurate in predicting mortality compared to frailty indexes based on both phenotypic model and multiple-deficits model at 32 and 70 items (Pilotto et al., 2012); 2) sensitive to changes of health and functional status during hospitalization (Volpato et al., 2016) and antidepressant treatments in outpatients (Pilotto et al., 2012a); 3) able to predict in-hospital length of stay for equal diagnosis (Volpato et al., 2015); 4) able to identify hospitalized elderly subjects who access homecare services, are institutionalized and/or re-hospitalized within one year from discharge (Pilotto et al., 2019b); 5) able to predict burden on healthcare resources and more problematic discharge allocation (Meyer et al., 2019a). All

these data suggest that MPI is an excellent diagnostic tool in terms of validity, reliability and feasibility for the management of older persons in clinical practice (Warnier et al., 2016).

8. Comprehensive Geriatric Assessment, prognosis and clinical strategies in elders

Recently, the international project MPI_AGE, cofounded by European Union, explored in deep the role of the CGA, and the derived MPI, as tool for guiding clinical decisions in vulnerable older adults with multimorbidity. Noteworthy, several clinical studies evaluated the appropriateness of few “critical” treatments in geriatric setting, like statin use in secondary prevention among people with diabetes mellitus (Pilotto et al., 2015) or with coronary artery disease (Pilotto et al., 2016b), anticoagulants in atrial fibrillation (Pilotto et al., 2016a), antidementia drugs in late-life cognitive impairment (Pilotto et al., 2018) or transcatheter aortic valve implantation (TAVI) in elderly patients with aortic stenosis (Bureau et al., 2017; van Mourik et al., 2019) and enteral tube feeding intervention in malnourished hospitalized older patients (Veronese et al., 2019a). Finally, recent literature has shown the use of the MPI could also extend to specific fields for personalized therapies such as for guiding immunotherapy in older patients with advanced malignancies (Sbrana et al., 2019) or in helping physicians in giving oral anticoagulants in older patients with non-valvular atrial fibrillation (Veronese et al., 2018a). Promising findings from these studies showed that in older adults the multidimensional approach warrants better clinical decisions (i.e. to treat or not to treat) depending on degree of multidimensional impairment of the subject (Pilotto et al., 2018a).

9. Prevention and treatment of frailty

In the English Longitudinal Study of Ageing, the Authors found a stepwise increase of frailty condition over time with greater prevalence in women compared to men. The analysis on 4638 respondents 65–89 years, followed-up every four years between 2004 and 2012, identified the following factors as potential predictors of future frailty: 1 chronic disease, 2 allostatic load based on measurement of nine biological and clinical biomarkers including blood pressure, anthropometric measurements, and blood tests for cholesterol levels, glucose control, and inflammatory markers, 3 low physical activity, 4 cognitive impairment and depressive symptoms, 5 poor social support (Ding et al., 2017).

These findings remark the need for health and socio-economic policies on preventive interventions targeting, in general population, these conditions that are highly relevant and potentially reversible predisposing factors to frailty. For example, it is now widely established, that physical activity not only is related to reduced physical frailty, but also improves physical performance in pre-frail subjects and in those at risk for sarcopenia (Piercy et al., 2018).

Also polypharmacy, namely the treatment with five or more medications daily, has been associated with higher frailty risk in elderly subjects (Veronese et al., 2017c). Deprescribing interventions, in accordance with well-accepted criteria, could reduce potentially

inappropriate medications and adverse drug events, optimizing management of frailty condition (Maclagan et al., 2017).

Growing evidence show a strict relationship between higher adherence to healthy diet, in particular Mediterranean diet, and lower incidence of frailty (Kojima et al., 2018; Veronese et al., 2018b). To support the multidimensional concept of frailty, however, in the “FRAIL” project, a prospective study carried out in older adults living in Genoa (the city with the highest ageing index in Europe), a lower prevalence of frailty was associated with higher quality of protein intake with diet (Cella et al., 2019), more physical activity, better economic conditions and higher levels of cultural fruition that, engaging in social and cultural events, fosters the growth of cultural interests, and social and affective interactions (Poli et al., 2017). All these finding suggest that the adoption of healthy lifestyle since youth and adulthood might help to prevent (and maybe to treat) frailty in older adults.

10. Future perspective

To date, identification, treatment and prevention of frailty represent a major challenge of geriatric science. Because of its multidimensionality, it is not surprising that frailty is not only a powerful risk factor for mortality but also profoundly affects response, effectiveness and tolerance to medical and surgical treatment and negatively influences quality of life (Hoogendijk et al., 2019; Kojima et al., 2016; Saum et al., 2014). Although specific tools for the assessment of frailty have been developed and validated, their clinical use is lingering because of their complexity and because their effectiveness in guiding a successful care plan is limited (Walston et al., 2019). Given the widespread application of the multidimensional approach in clinical practice, we suggest that at this stage CGA could be used to identify “frailty” and use this information to improve the overall management of frail older adults. It is possible that in future new, more effective tools may be developed and their efficacy in the specific management of frailty can be demonstrated. Until then, CGA is a valid alternative.

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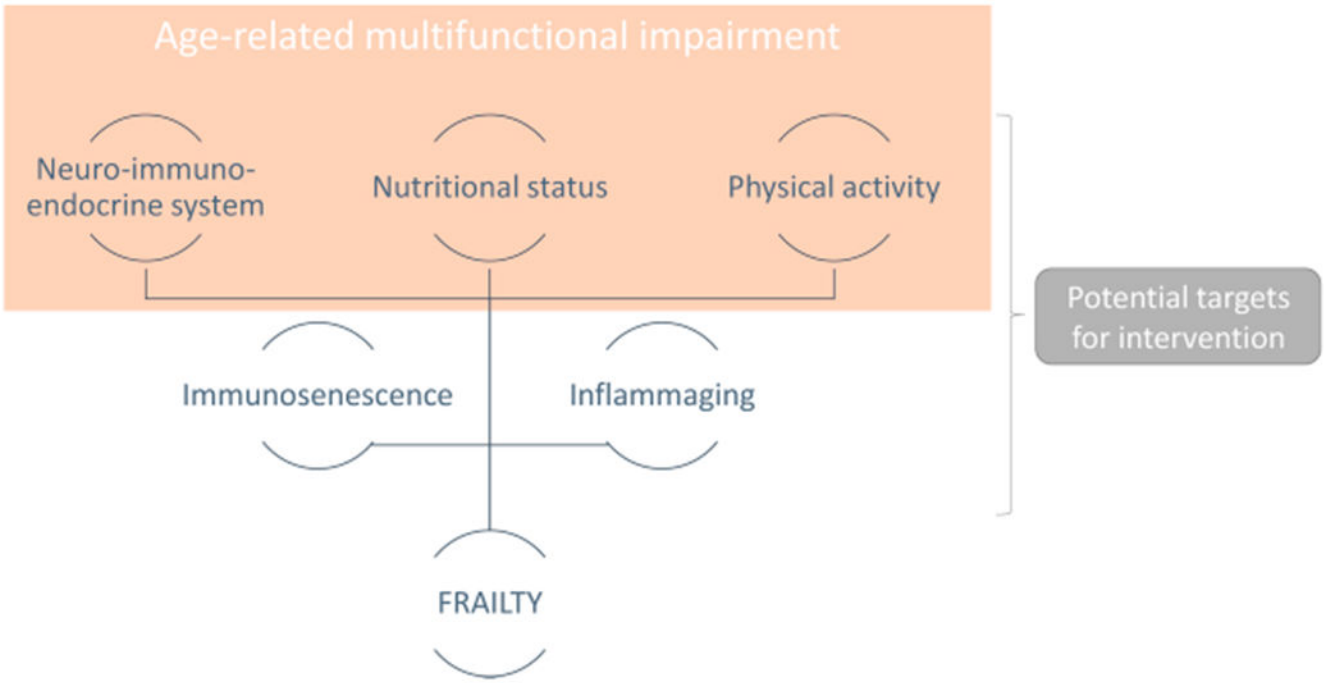

Fig. 1.
The underlying mechanisms of frailty.

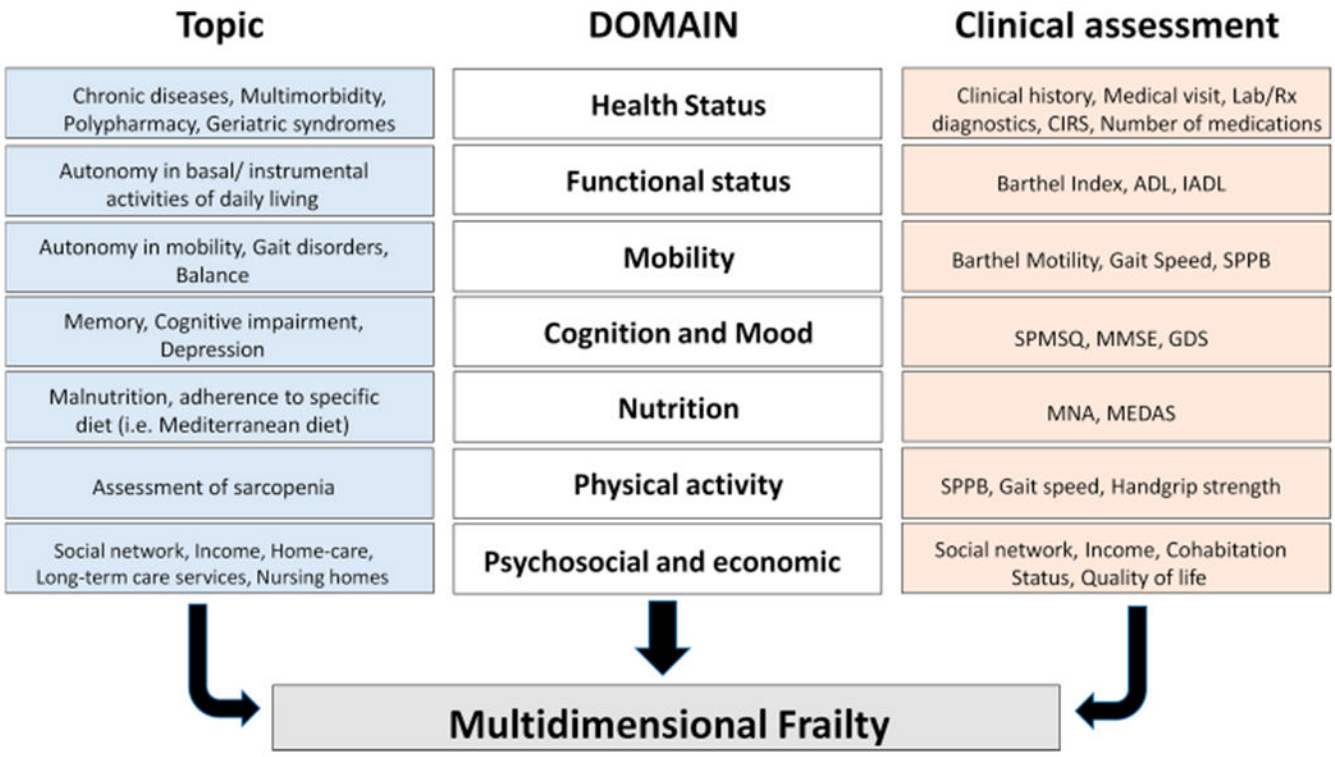

Fig. 2.

Domains of the multidimensional model of frailty.

Abbreviations: ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; CIRS: Cumulative Illness Rating Scale; GDS: Geriatric Depression Scale; MEDAS: Mediterranean Diet Adherence Screener; MMSE: Mini Mental State Examination; MNA: Mini Nutritional Assessment; SPMSQ: Short Portable Mental State Questionnaire; SPPB: Short Physical Performance Battery.

Table 1

The frailty model according three overlapping dimensions: biological, physiopathological mechanisms and clinical features.

Biological mechanisms	Mitochondrial dysfunction Oxidative stress DNA damage Shortening of telomere length Defective autophagy DNA methylation Stem cells exhaustion Chronic low-grade inflammation
Pathophysiologic	Neurodegeneration Anabolic deficiency Energetic imbalance Reduced protein synthesis
Clinical features	Functional deficits in activity of daily living Reduced mobility Cognitive impairment Malnutrition Sarcopenia Multimorbidity Polypharmacy Geriatric syndromes

Table 2

Clinical studies using the CGA-based Multidimensional Prognostic Index (MPI).

Tool	Setting	Outcomes and Diseases	Study type	Number of participants	Main findings
MPI 8 domains 63 items	Hospital	All-cause mortality at 6-12 months	Prospective cohort study (Brunet et al., 2019; Bryant et al., 2019; De Luca et al., 2015; Pilotto et al., 2008)	3,236	MPI accurately stratifies the risk of 6- and 12-month mortality; MPI at admission and at discharge is equally predictive of 12-month mortality
		All-cause mortality at 3-5 years	Prospective cohort study (Jung et al., 2016)	1,109	MPI stratifies the risk of 3- and 5-year mortality
		In hospital mortality and length of stay	Multicenter prospective cohort studies (FIRI-SIGG Study Group (Pilotto et al., 2016c), MPI_TriVeneto Study Group (Volpato et al., 2015)) and single center prospective cohort study (De Luca et al., 2015)	3,902	MPI at admission is an independent predictor of in-hospital death and length of stay
		MPI change during hospitalization	Multicenter prospective cohort study (MPI_TriVeneto Study Group) (Volpato et al., 2016)	960	MPI decreases for patients with short hospitalization (1-6 days) and tendes to increase for those with longer lenght of stay
		Dementia	Prospective cohort study (Pilotto et al., 2009c)	262	MPI predicts 1-, 6-, and 12-month mortality in hospitalized elderly patients with dementia
		Late-life depression	Prospective cohort study (Pilotto et al., 2012a)	485	MPI decreases after treatment with selective serotonin reuptake inhibitors in late-life major depressive disorder
		Gastrointestinal bleeding	Prospective cohort studies (Pilotto et al., 2009a; Pilotto et al., 2007)	127	MPI predicts short- and long-term mortality in older patients with upper gastrointestinal bleeding; Greater accuracy than organ-specific prognostic indices (Rockall and Blatchford scores); MPI predicts the risk of 2-year mortality in elderly patients with upper gastrointestinal bleeding
		Liver cirrhosis	Prospective cohort study (Pilotto et al., 2009a)	154	MPI predicts short- and long-term mortality in older patients with liver cirrhosis; Greater accuracy than Child-Plugh score
		Femoral and hip fracture	Prospective cohort study (Musacchio et al., 2018; Sciume et al., 2018), retrospective cohort study (Ortho-MPI) (Vitale et al., 2014)	422	MPI predicts 6-month mortality among elderly patients with hip or neck femur fractures; MPI is an independent predictor of the waiting time to surgery in older patients with hip fracture
		Chronic kidney disease	Prospective cohort study (Pilotto et al., 2012c), cross-sectional cohort study (Aucella et al., 2012)	1,360	Adding MPI to the estimated glomerular filtration rate (eGFR) improves the prediction of 2-year all-cause mortality in older patients with chronic kidney disease; Hemodialysis elderly patients have higher MPI scores compared to geriatric patients without renal failure
		Pneumonia	Prospective cohort studies (Pilotto et al., 2009b, 2018b, 2018c)	233	MPI predicts mortality risk at 30 days, 6 months, and 12 months in older patients with community-acquired pneumonia; Greater accuracy than pneumonia severity index; Adding procalcitonin or proadrenomedullin levels to admission MPI increases the prognostic accuracy for 1-month mortality

Tool	Setting	Outcomes and Diseases	Study type	Number of participants	Main findings
		Cardiovascular disease	Prospective cohort study (Carriere et al., 2018)	216 (¾ 80 years old)	MPI independently predicts 1-year mortality in elderly patients with cardiovascular diseases; Adding serum creatinine and albumine to MPI increases the prognostic accuracy
		Heart failure	Prospective cohort study (Pilotto et al., 2010)	376	MPI predicts 1-month mortality in older patients with heart failure; Greater accuracy compared to the New York Heart Association, the Enhanced Feedback for Effective Cardiac Treatment, and the Acute Decompensated Heart Failure National Registry regression model scores
		Transient Ischmic Attack (TIA)	Prospective cohort study (Sancarlo et al., 2012)	654	MPI predicts 1-, 6-, and 12-month mortality in older patients hospitalized for TIA
		Cancer	Prospective cohort study (Giantin et al., 2018)	160	MPI predicts 12-month mortality in elderly patients with locally-advanced or metastatic solid cancers
		Peripheral artery disease	Two-center prospective cohort study (Drudi et al., 2019)	148	MPI does not predict mortality and worsening disability at 12 months after interventions for peripheral artery disease
	Ambulatory care	Cognitive impairment and dementia	Cross-sectional cohort studies (Amanzio et al., 2017; D'Onofrio et al., 2016), prospective cohort studies (Coin et al., 2012; Gallucci et al., 2014), pilot single-blind randomized controlled clinical trial with rivastigmine (D'Onofrio et al., 2015)	930	MPI is associated with cognitive and behavioural domains, and impaired awareness for instrumental activities disabilities in people with cognitive deficits; Alzheimer's disease (AD) patients with delusions have higher MPI scores compared to those without delusions; MPI increases over 12-month follow-up in elderly patients with untreated dementia and BMI ¼ 25 kg/m^2; MPI predicts the risk of death and of hospitalizations in outpatients with cognitive impairment; Rivastigmine transdermal patch and cognitive stimulation in AD patients improve MPI at 6-month follow-up
		Type 2 diabetes mellitus	Multicenter cross-sectional cohort study (Metabolic Working Group) (Noale et al., 2016)	1,342	Diabetic elderly patients receiving polypharmacy (>5 medications/ day) have higher MPI scores
		Dysthyroidism	Prospective cohort study (Pasqualetti et al., 2018)	643	Reduction of FT3/FT4 ratio is associated with higher MPI scores
		Cancer	Prospective cohort study (Onco-MPI) (Brunello et al., 2016)	658	Onco-MPI accurately predicts 1-year mortality in older cancer patients
	Nursing home	Overweight and obese	Prospective cohort study (Pizzato et al., 2015)	161	People with BMI ¼ 25 kg/m^2 and weight loss have the worst decline in the MPI over 1-year follow-up
	Community-dwelling	Survival at 12 years Days in hospital during 10 years	Prospective population-based study (SNAC-K study) (Angleman et al., 2015)	2,472	Higher MPI scores are associated with more days in hospital and with reduced survival, across different age groups
		Falls in older adults with knee osteoarthritis	Prospective cohort study (Osteoarthritis Initiative) (Veronese et al., 2019b)	885	Higher MPI scores are associated with increased risk of recurrent falls over 8-year follow-up
8 domains 53 items	Hospital	All-cause mortality at 1-12 months	Prospective cohort study (Sancarlo et al., 2011)	4,088	MPI accurately stratifies the risk of 1- and 12-month mortality
8 domains 53 items		In-hospital mortality All-cause mortality at 1 year Institutionalization at 1 year Access to homecare services	Multicenter prospective study (MPI_AGE) (Pilotto et al., 2019b)	1,140	Higher MPI scores are associated with higher risk of overall mortality, institutionalization, rehospitalization, and access to home care services during 12 months

Tool	Setting	Outcomes and Diseases	Study type	Number of participants	Main findings
		at 1 year Re-hospitalization at 1 year			
		Geriatric syndromes and resources	Cross-sectional cohort study (Meyer et al., 2019)	135	Fewer geriatric syndromes and a higher number of geriatric resources are significantly correlated with lower MPI scores
		Burden on healthcare resources and allocation at discharge	Prospective cohort study (Meyer et al., 2019a)	135	MPI is significantly related to grade of care and length of hospital stay; Patients with higher MPI scores are more often transferred from other hospital settings and less likely to be discharged home
		Atrial fibrillation	International multicenter prospective cohort study (EUROSAF) (Quispe Guerrero et al., 2019)	1,281 (study ongoing)	The use of oral anticoagulants seems to decrease the risk of death at 1 year compared to people not taking anticoagulants; The effect seems to be stronger in people with lower MPI
		Patients undergoing transcatheter aortic valve implantation (TAVI)	Prospective cohort study (Bureau et al., 2017), international multicenter prospective registry (van Mourik et al., 2019)	187	MPI accurately predicts 6-, and 12-month mortality in elderly patients undergoing TAVI; MPI predicts the likelihood of combination of death and/or non-fatal stroke by 12 months after TAVI in elderly patients
		Mortality risk associated with enteral tube feeding	Multicenter retrospective cohort study (Veronese et al., 2019a)	1,064	Patients with enteral tube feeding and higher MPI scores have higher 1-year mortality
	General practice	Grade of care Hospitalization rate Mortality at 1 year Nursing home admission Use of home care services Falls Number of general practitioner contacts, of geriatric resources and geriatric syndromes	Prospective cohort study (Meyer et al., 2019c)	135	MPI is strongly associated with adverse outcomes in older patients and predicts the number of general practitioner contacts over 1 year follow-up
MPI-SVaMA 9 domains	Community-dwelling	All-cause mortality	Prospective cohort study (Pilotto et al., 2013)	12,020	MPI-SVaMA accurately stratifies the risk of 1- and 12-month mortality
		Dementia	Multicenter retrospective cohort study (Pilotto et al., 2018)	6,818	Use of antidementia drugs is associated with reduced 2-year mortality in elderly patients with lower MPI-SVaMA scores
		Type 2 diabetes mellitus	Multicenter retrospective cohort study (Pilotto et al., 2015)	1,712	Statin treatment is associated with reduced 3-year mortality independently of age and MPI-SVaMA in elderly patients with diabetes mellitus
		Atrial fibrillation	Multicenter retrospective cohort study (Pilotto et al., 2016a)	1,827	Warfarin treatment is significantly associated with lower 2-year mortality in elderly patients with atrial fibrillation, irrespective of MPI-SVaMA group
		Coronary artery disease	Multicenter retrospective cohort study (Pilotto et al., 2016b)	2,597	Statin treatment is associated with lower 3-year mortality risk in elderly patients with coronary artery disease, irrespective of age and MPI-SVaMA group
SELFY-MPI 8 domains Self-administered	Ambulatory care	Any disease	Cross-sectional cohort study (EFFICHRONIC) (Pilotto et al., 2019a)	167 (¾18 years old)	SELFY-MPI shows high agreement with MPI irrespective of age groups

Tool	Setting	Outcomes and Diseases	Study type	Number of participants	Main findings
		HIV + patients	Cross-sectional cohort study (Mora et al., 2019)	50	SELFY MPI (i.e. quality of life and cognitive functions) is associated with the laboratory exam's parameter TCD4+ and viral load in senior HIV + patients
	Community-dwelling	Any disease	Multicenter cohort study EFFICHRONIC (Zora et al., 2019)	310 (>18 years old)	SELFY-MPI shows a very good feasibility demonstrating potential usefulness both as a screening and an outcome measure tool