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POSITION PAPER

Heart Failure Association of the European Society of Cardiology position paper on frailty in patients with heart failure

Cristiana Vitale[1]*, Ewa Jankowska[2], Loreena Hill[3], Massimo Piepoli[4,5], Wolfram Doehner[6], Stefan D. Anker[7], Mitja Lainscak[8], Tiny Jaarsma[9], Piotr Ponikowski[2], Giuseppe M.C. Rosano[1], Petar Seferovic[10], and Andrew J. Coats[1]

[1]Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy; [2]Department of Heart Diseases, Wroclaw Medical University, Centre for Heart Diseases, Military Hospital, Wroclaw, Poland; [3]School of Nursing and Midwifery, Queen's University, Belfast, UK; [4]Heart Failure Unit, Cardiology, Guglielmo da Saliceto Hospital, Piacenza, Italy; [5]Institute of Life Sciences, Scuola Superiore Sant'Anna, Sant'Anna School of Advanced Studies, Pisa, Italy; [6]Department of Cardiology (Virchow Klinikum), German Centre for Cardiovascular Research (DZHK), partner site Berlin, and BCRT - Berlin Institute of Health Center for Regenerative Therapies, and Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [7]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [8]Faculty of Medicine, University of Ljubljana and Department of Internal Medicine, General Hospital Murska Sobota, Ljubljana, Slovenia; [9]Facutly of Medical and Health sciences, Linköping University, Linköping, Sweden; and [10]Faculty of Medicine, University Medical Center Belgrade, Belgrade, Serbia

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Heart failure (HF) and frailty are two distinct yet commonly associated conditions. The interplay between the two conditions is complex, due to overlaps in underlying mechanisms, symptoms and prognosis. The assessment of frailty in patients with HF is crucial, as it is associated with both unfavourable outcomes and reduced access and tolerance to treatments. However, to date a consensus definition of frailty in patients with HF remains lacking and the need for a validated assessment score, for identifying those HF patients with frailty, is high and timely. This position paper proposes a new definition of frailty for use by healthcare professionals in the setting of HF and creates a foundation for the design of a tailored and validated score for this common condition.

Keywords Heart failure • Frailty • Aging • Instruments • Score

Introduction

The European Society of Cardiology (ESC) guidelines on heart failure (HF) suggest that healthcare professionals should 'monitor frailty and seek and address reversible causes (cardiovascular and non-cardiovascular) of deterioration in frailty score in elderly patients'.[1] The increasing evidence concerning the importance of frailty in HF patients and the lack of a validated instrument to correctly identify it have both highlighted the need for a position paper to improve clarity on the role of frailty in HF.

This executive document reflects the key points of a meeting organised by the Heart Failure Association (HFA) of the ESC on the topic 'Frailty in heart failure'. Aims of this meeting were: (i) to identify a consensus definition of frailty in patients with HF; (ii) to build a common understanding concerning the importance of the assessment of frailty in HF patients; (iii) to identify the main domains of a new score, the HFA Frailty Score, specifically tailored for HF patients.

Although the concept of frailty is extensively used, in clinical and research settings, an internationally accepted definition is still lacking and there is no agreement on which is the best method or instrument to assess frailty. Several definitions of frailty and a plethora of different instruments have been used for the identification of frailty within a variety of disease states and settings.[2–8] This has limited the possibility not only to 'speak a common language' and to compare the results from different studies, but has challenged the possibility for correct diagnosis and interventions. In addition, the lack of a gold standard method

*Corresponding author. Centre for Clinical & Basic Research, IRCCS San Raffaele Pisana, Via della Pisana 235, 00163 Rome, Italy. Tel: +39 06 52252409, Fax: +39 06 52255567, Email: cristiana.vitale@gmail.com

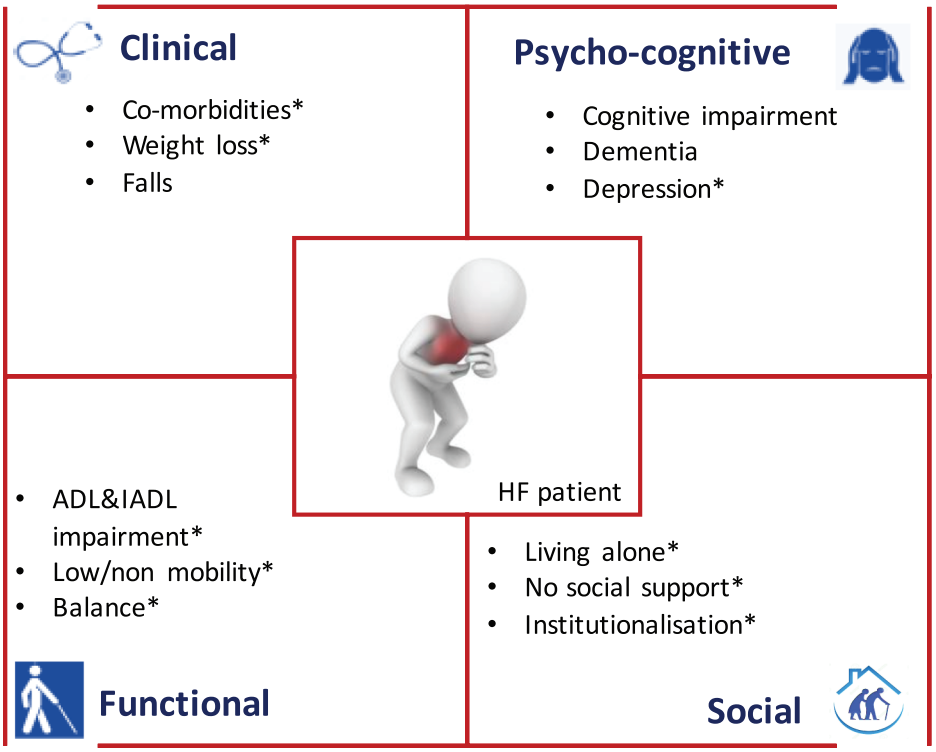

Figure 1 The four main domains – clinical, physical-functional, cognitive-psychological, and social – defining the Heart Failure Association (HFA) Frailty Score. Reversible and/or treatable variables are identified by asterisks. ADL, activities of daily living; HF, heart failure; IADL, instrumental activities of daily living. Adapted from Gorodeski *et al.*[9]

and the inconvenience of using a number of available assessment instruments (due to time, availability of special equipment, patient limitations, etc.) have limited the routine assessment of frailty in daily practice. This has facilitated the use of the clinical subjective judgments (eyeball test or foot-of-the-bed assessment) to define frailty in busy HF clinical settings.[2]

The presence of a complex overlap between frailty and HF, the emerging and increasing data on the prognostic role of frailty as well as the interference of frailty with the possible treatments for HF patients form the basis for the need of a validated diagnostic and predictive assessment score tailored for patients with HF.

As the HFA strongly believes that a holistic approach is more reliable than the physical approach in recognising those patients with HF that are also frail, it convened a workshop to both devise a new definition of frailty in HF and to design a new HF frailty assessment score, the HFA Frailty Score.

This new score has been built considering four domains – clinical, physical-functional, cognitive-psychological and social – as the main determinants of frailty in HF patients (*Figure 1*).

These four domains have been suggested by Gorodeski and colleagues[9] as the main contributors of health outcomes to consider in older adults with HF. However, although Gorodeski and colleagues consider frailty as only one of the determinant of the physical domain, HFA believe that all these four domains have to be incorporated as determinants of the proposed new HF frailty score as they well reflect the holistic approach of the HFA score.

Overview of frailty definition and assessment tools

Frailty is commonly considered a biologic or geriatric syndrome characterised by a state of increased vulnerability to endogenous and exogenous stressors, due to age-related declines in physiologic reserve and function across multiple physiologic systems.[4] This increased vulnerability contributes to higher risk of falls, institutionalisation, disability, and death.

Although several conceptual definitions of frailty have been used in medicine, the available instruments to evaluate frailty derive from two basic concepts of frailty: the physical frailty phenotype[4] and the cumulative deficit model.[5,6]

The physical frailty phenotype, proposed and validated by Fried and colleagues in community dwelling older adults in the Cardiovascular Health Study,[4] described frailty as a biological syndrome that causes age-related physical decline, in which three or more of the following physical components are present: unintentional weight loss [>10 lbs (4.5 kgs) in the last year]; self-reported exhaustion; weakness (reduced handgrip strength); slow walking speed (time in seconds – usual pace – over 15 ft); low self-reported physical activity. A pre-frail status is accordingly when one or two criteria

are present, identifying an individual at high risk of progressing to frailty.

The cumulative deficit model, proposed and validated by Rockwood and colleagues in community dwelling older adults in the Canadian Study of Health and Aging,[5,6] described frailty as a state of vulnerability, resulting from an accumulation of a range of individual impairments and conditions, thus creating a frailty index. The deficit model is a more comprehensive instrument than the frailty phenotype. According to a multidimensional (holistic) approach, it assesses the accumulation of health deficits across multiple domains, such as cognition, activities of daily living, co-morbid diseases, deficits of social relations and social support, or abnormal laboratory results. All these health deficits interact with each other, with still not adequately understood mechanisms, to determine the occurrence of frailty. The frailty index is expressed as a ratio of health deficits present to the total number of deficits considered; the greater the number of health deficits, the higher the degree of frailty.

Although both the Fried phenotype and the cumulative index definitions have been widely used and have demonstrated their predictive value, their routine use in the daily practice is limited by major weaknesses. Among these, the difficulty in defining the unintentional weight loss in patients taking diuretics or the possible floor effect related to the instrument focused on physical frailty can be particularly relevant in patients with HF (*Table 1*).

In an attempt to overcome these weaknesses, several other instruments have been developed over time, through changing, omitting or adding criteria to one or the other of these two conceptual definitions or using single components of the physical frailty phenotype.[2–17] The main characteristics and limitations of the main frailty assessment instruments used in HF patients are shown in *Table 1*.

Recently, Sze *et al.*,[18] comparing three of the main frailty instruments (Fried phenotype, Deficit Index and Edmonton Frailty Score) used in HF, found that fewer than half of those patients classified as frail with one of the frailty instruments were similarly classified as frail when all the three different instruments were used simultaneously. This reinforces the need for a new instrument to better identify frail patients with HF.

Frailty in heart failure

Frailty is more prevalent in HF than the general population. The estimated overall prevalence of frailty in HF is around 45%, with a lower prevalence in studies using the physical frailty assessment tool compared to those using the cumulative deficit approach (42.9% vs. 47.4%).[19] Patients with HF are up to six times more likely to be frail, and frail people have a significantly increased risk of developing HF.[20,21]

Although both frailty and HF are common in older adults, the prevalence of frailty in patients with HF is independent of age, as frailty can be experienced also by younger (<60 years) patients with HF.[20] This suggests that frailty in HF patients is not solely related to, and it is in fact additive to, the progressive age-related decline in physiological reserve.

Conversely to what it may be thought, frailty seems more common in patients with HF with preserved ejection fraction (HFpEF) than in those with reduced ejection fraction (HFrEF), this possibly related to the greater burden of cardiac and non-cardiac co-morbidities typically experienced by patients with HFpEF.[22]

The relation between the New York Heart Association functional class and the prevalence of frailty is not clear as some studies found a poor association[4,19,23] while others a linear correlation.[18,24] This can be probably related to the methods used for the assessment of frailty.

The overlap between frailty and HF is complex and each syndrome may mimic the other. Although the precise mechanisms of frailty in HF have not been fully elucidated, HF patients share with frail patients pathophysiological, clinical and non-clinical aspects, which have important consequences for their prognosis and management.

Pathophysiology

Pathophysiological pathways common to both HF and frailty appear to involve a multisystem cascade that includes disorders and dysregulation in neuro-hormonal, metabolic, inflammatory, and immunologic pathways. This cascade leads to an enhanced catabolic state, energy failure, oxidative stress, and release of pro-inflammatory signals.[25–27] The up-regulation of inflammatory biomarkers impairs hormones, such as cortisol and growth hormone, which contributes to downstream effects and leads to an enhanced catabolic state, thus favouring the occurrence of frailty.

The imbalance between anabolic and catabolic state in HF may also exacerbate the decline in muscle mass and strength, favouring the occurrence of sarcopenia, cachexia, and frailty.

However, the multiple complex and interrelated pathogenic mechanisms that adversely affect frailty and HF remain poorly understood and cannot be limited only to the physical consequences of frailty.

Clinical aspects

The typical clinical aspects of HF, especially in its advanced stages, overlap considerably with the manifestations of 'physical' frailty: exercise intolerance, weakness, fatigue, and exhaustion. Reduced lean muscle mass (sarcopenia) and sometimes cachexia may be associated with both conditions.[28]

Nevertheless, physical impairment, often considered a synonymous of frailty, is only one of the aspects characterising frailty and several other clinical and non-clinical conditions, such as depression, cognitive impairment, malnutrition, anaemia, dependency, isolation and/or lack of social support are commonly found in both HF and frail patients.

Prognosis

The presence of frailty has a negative impact on the prognosis of patients with HF. Frailty accelerates the progression of HF and increases morbidity and mortality in these patients.[24,29–31] Frailty

Table 1 Main instruments to identify frailty in heart failure

Frailty assessment instrument	Characteristics	Limitations in HF patients
Physical frailty		
Fried's Frailty Phenotype (FP)[4]	Five physical components of frailty: weakness (handgrip dynamometer); slow walking speed (5 m gait speed); exhaustion; unintentional weight loss; low physical activity	- Only focus on physical frailty - Need of dynamometer - Possible floor effect in HF patients - Difficulty in assessing unintentional weight loss in HF patients taking diuretics
Single item or modified version of FP[9–11]	- Single-item components of the FP - Modified FP: i.e. 3 m gait speed, self-reported measures of appetite instead of weight loss	- Only focus on physical frailty - Possible need of dynamometer - Possible floor effect in HF patients - High misclassification rate
Short Physical Performance Battery (SPPB)[12,13]	Encompasses slowness, weakness, and balance measured by a series of three timed physical performance tests (gait speed, chair stand test, and tandem balance)	- Only focus on physical frailty - Possible floor effect in HF patients
Multidimensional frailty		
Frailty Index of Accumulative Deficits (FI-CD) (Rockwood's approach)[6]	- Assessed through the accumulation of health deficits across multiple domains, such as cognition, activities of daily living, co-morbid diseases, deficits of social relations and social support, or abnormal laboratory results	- Time consuming for routine use - Value expressed as a ratio of health deficits present to the total number of deficits considered
FI-CGA[14]	- Frailty index derived from clinical records or the Comprehensive Geriatric Assessment (FI-CGA) performed in elderly people	
Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS)[6,15]	Seven-point frailty scale with a written description of frailty based on disability for basic and instrumental activities of daily living, mobility, activity, energy, and disease-related symptoms and complemented by a visual chart to assist with the classification of frailty based on clinical judgement	- Semi-quantitative and based on clinical judgement - Heavily influenced by the patient's level of disability - Possible floor effect in HF patients
Edmonton Frailty Scale (EFS)[16]	Contains nine components: cognition (clock test), general health status (number of hospitalisation in the last year), functional independence, social support, medication use, nutrition (weight loss), mood, continence, functional performance (timed get up and go) - It is a simplified multidimensional frailty assessment tool	- Low sensitivity - Risk of misclassification

HF, heart failure.

contributes to a higher risk of mortality at 1 year, increased HF hospitalisations with longer bed days in hospital, and a decreased probability of surviving more than 10 years.

In addition, frailty reduces the resistance of patients with HF to myocardial ischaemia, pressure and volume overload, and it also increases the risk of arrhythmias, causing decompensation and rapid functional deterioration.[32,33]

The physical components of frailty are not the only recognised as negatively affecting the outcomes of HF patients. The OPERA-HF (Observational registry to assess and PrEdict the in-patient course, risk of Re-Admission and mortality for patients hospitalized for or with Heart Failure) study has shown that psycho-social factors, such as depression or anxiety, cognitive impairment and living alone are all strongly associated with negative near-term outcomes in patients with HF, such as unplanned recurrent readmissions, 30-day outcome after an admission for HF, and mortality following an admission to hospital for HF.[34]

Furthermore, in advanced HF, frailty is an independent predictor of increased all-cause mortality and adverse outcomes (longer recovery time and increased risk for rehospitalisation), as shown in patients referred for heart transplantation or left ventricular assist device implantation.[11,35–38]

Therefore, frailty is a strong and independent predictor of negative outcomes and is associated with greater healthcare utilisation in HF patients.[39]

The addition of the frailty score to the Meta-analysis Global Group in Chronic HF (MAGGIC) risk score, one of the most predictive scores in HF,[40] results in a significant improvement in risk classification of HF patients,[41] thus suggesting that frailty defines a risk not yet captured by traditional risk scores.

Treatment

The presence of frailty in patients with HF, especially in those with advanced HF, has an unfavourable impact on the range of possible treatments and interventional options. Due to the increased risk of adverse events and negative outcomes, some interventions (i.e. devices, transplantation, etc.) can become under-utilised for those patients with advanced HF that are frail. In this perspective, similar to ageism,[42] a diagnosis of frailty may become a

discriminative factor ('frailtyism' – definable as a stereotyping, prejudice, and discrimination against people on the basis of the presence of frailty) in the management of these patients, who are more likely to receive less standard HF treatments as a result. This risk is also increased by the lack of evidence-based criteria to help and guide the management of HF patients with frailty.

Therefore, the use of an objective and easy to apply measurement of frailty in clinical practice, rather than a 'vague' clinician's subjective 'doorway assessment', will help clinicians to better identify those HF patients that being effectively frail may face a higher risk of negative outcomes.

Therefore, due to its prognostic and therapeutic implications, the identification of frailty is of uttermost importance in the daily assessment and management of patients with HF.

Requirement for a new definition and a tailored assessment score of frailty in heart failure

In patients with HF, frailty is perceived as a reversible/dynamic state of increased vulnerability to stressors in one or more clinical and non-clinical domains, with consequential negative outcomes and dire prognosis. The occurrence of a stressor (acute/chronic, internal/external), even though apparently insignificant for a healthy person, such as a minor acute infection, an imbalance in a 'chronic' disease, a new medication or a minor procedure,[43] could potentially alter the precarious equilibrium within one or more domains of the HF patients' health status. This results in a disproportionate individual response or decompensation associated with negative outcomes, such as increased morbidity, increased healthcare use (hospitalisation, prolonged recovery, institutionalisation, etc.), greater dependency, and higher risk of mortality.

Although both frailty and HF are common in elderly patients with prevalence increasing with age, frailty must not be considered neither as a 'progressive age-related decline in physiological reserve and function' (according to the World Health Organisation)[44] nor as a 'geriatric syndrome'. This is supported by the lack of any unidirectional correlation between the prevalence of frailty in HF patients and their age.[7] All patients with HF, independent of their chronological age, are at risk of frailty, but not all elderly patients with HF are inevitably frail. Consequently, chronological age cannot represent a parameter to guide the assessment of frailty, and all patients with HF should be evaluated for the presence of frailty, independently of their age, in order to better stratify their risk.

Therefore, the HFA suggest that frailty should be defined in patients with HF as a *multidimensional dynamic state, independent of age, that makes the individual with HF more vulnerable to the effect of stressors*. The dynamic interrelations of clinical and non-clinical conditions (multidimensional), that can be reversible (treatable) or irreversible (supportive care), interact each other to determine a state of vulnerability (frailty). This definition reflects two key concepts: first in patients with HF, frailty can be better identified using a holistic multidimensional approach than the physical phenotype approach; second the identification and treatment of those parameters that are modifiable or reversible may improve the outcomes of frail HF patients.

Physical frailty is only one of the domains of frailty and in patients with HF the use of this sole approach can result in patient misclassification due to a so-called floor effect. Functional limitations, due to decreased exercise tolerance and shortness of breath, are common in HF patients and are influenced by HF severity and aging. As not all HF patients with reduced functional capacity are frail, other clinical and non-clinical domains require consideration to correctly identify those HF patients with frailty.

Therefore, the HFA Frailty Score has been built on four main domains – clinical, functional, psycho-cognitive and social – that are considered the determinants of frailty in HF patients (*Figure 1*).

The *clinical domain* takes into consideration the number and type of co-morbidities, as in HF patients some co-morbidities can have a higher prognostic weight than others and, therefore, greater influence on the therapeutic decisions (i.e. use of class 1 drugs such as renin–angiotensin system inhibitors in some patients with severe renal dysfunction, use of implantable cardioverter-defibrillator, etc.).[1] Co-morbidities, in turn, are associated with poly-therapy, increased risk of inappropriate prescribing, higher risk of adverse events, falls, and hospitalisations. Therefore, as mentioned in the latest ESC HF guidelines the 'management of co-morbidities is a key component of the holistic care of patients with HF'.[1]

Although the presence of cognitive impairment and mood disturbances, such as depression, could have been generically considered as co-morbidities, due to their consequences on health status, prognosis and weight in determining a frail status, they have been included in a separate domain (*psycho-cognitive domain*). Both cognitive impairment and depression may also contribute to poor adherence, poor prognosis, and social isolation.

In parallel physical impairment, often associated in HF patients with a global imbalance between the anabolic and catabolic state that may lead to sarcopenia and, eventually, body wasting with cachexia, can cause dependency, incapacity to perform activities of daily living and/or instrumental activities of daily living, and higher risk of falls. Therefore, the functional status of HF patients has been identified as a separate domain (*functional domain*).

Although the clinical and functional factors may have negative consequences on the social aspect of life, it is also true that the presence of isolation and the lack of support (caregiver) interfere with the access to care and can influence the prognosis of frail patients. Therefore, it has been identified as a *social domain*.

The variables included in the four main domains, in turn, cause a complex cascade of factors such as poly-therapy, dependency, higher risk of hospitalisations, negative outcomes, and with some variables overlapping across the four main domains. This overlap reflects the holistic nature of frailty, involving the individual in all its entirety and suggests the possibility that the treatment of single variables can potentially reverse the status of vulnerability. This is supported by the finding that the composite elements of the frailty phenotype have an incremental value in predicting mortality than the individual elements of frailty.[41]

Table 2 Characteristics of the proposed Heart Failure Association Frailty Score

- Easy to use in busy clinical settings
- Quick to perform
- No need for special equipment
- Cheap
- Reliable: able to accurately identify heart failure patients that are frail in daily practice
- With minimal distress or concern caused to the patient
- Predictive: able to correlate with prognosis and predict adverse clinical outcomes

In addition, the novel bespoke HFA Frailty Score aims to overcome the limitations of the available scores, satisfying all the essential requisites (*Table 2*), which will help in daily use of this score within busy healthcare settings.

Future directions

The HFA Frailty Score will be the first instrument specifically developed to identify frailty in the HF population. This, and the consensus definition of frailty in HF patients, should help fill the gap in both clinical and research settings.

The definition of the new score is only the first step. The next following steps will be: (i) to agree with a multidisciplinary panel of experts the specific items to include in the four domains of the HF Frailty Score, using the consensus Delphi method; (ii) to demonstrate that the new score is both specific and sensitive in identifying patients with frailty in HF cohort studies (acute and chronic HF).

The aim of the new score, therefore, will be to have the most accurate (adequate identification of those patients with HF that are also frail) and predictive tool to diagnose frailty in HF. This will help to design an individualised monitoring and treatment plan, including rehabilitation, occupational therapy, social support, HF self-care, thus reducing and/or preventing the occurrence of negative outcomes in frail patients with HF.[45,46] Indeed, the new score will enable those HF patients identified as frail to 'benefit from closer contact with the HF specialist team, more frequent follow-up and monitoring and individualised self-care support'.[1] Finally, the score should also allow for adequate management strategies research. It should be able to pick up the management effects which could switch the patient from frail to non-frail, make them less frail in individual or all domains, or to improve outcomes in frail patients.

Conclusions

The increased complexity of patients with HF and their longer life expectancy has modified the scenario of HF. Frailty should no longer be considered synonymous with aging, furthermore not all patients with HF can be considered frail.

Frailty is a dynamic and partially reversible state, consisting of four main domains, some modifiable components beyond non-reversible ones. Recognising these components may guide management and improve HF outcomes. An accurate assessment is the first and crucial step for a tailored and individualised healthcare management programme in patients with HF and frailty.

Routine frailty assessment for HF patients should be included in daily clinical practice as the identification of frailty could help in risk stratification, decision-making, design of an individualised patient care plan, reduce/prevent negative outcomes, reduce health costs. The HFA Frailty Score will be the first score specifically designed for and validated within a HF population.

Conflict of interest: none declared.

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