

Heart Failure and Problems with Frailty Syndrome: Why it is Time to Care About Frailty Syndrome in Heart Failure

Izabella Uchmanowicz,¹ Agnieszka Młynarska,² Magdalena Lisiak,¹ Marta Kałużna-Oleksy,³ Marta Wleklik,¹ Anna Chudiak,¹ Magdalena Dudek,³ Jacek Migaj,³ Lynne Hinterbuchner⁴ and Robbert Gobbens^{5,6,7}

1. Department of Clinical Nursing, Faculty of Health Science, Wrocław Medical University, Poland; 2. Department of Gerontology and Geriatric Nursing, School of Health Sciences, Medical University of Silesia, Poland; 3. Department of Cardiology, Poznan University of Medical Sciences, Poland; 4. Department for Internal Medicine and Cardiology, Salzburg University Hospital, Austria; 5. Faculty of Health, Sports and Social Work, Inholland University of Applied Sciences, Amsterdam, the Netherlands; 6. Zonnehuisgroep Amstelland, Amstelveen, the Netherlands
7. Department of Primary and Interdisciplinary Care, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

Abstract

Frailty syndrome (FS) is an independent predictor of mortality in cardiovascular disease and is found in 15–74% of patients with heart failure (HF). The syndrome has a complex, multidimensional aetiology and contributes to adverse outcomes. Proper FS diagnosis and treatment determine prognosis and support the evaluation of treatment outcomes. Routine FS assessment for HF patients should be included in daily clinical practice as an important prognostic factor within a holistic process of diagnosis and treatment. Multidisciplinary team members, particularly nurses, play an important role in FS assessment in hospital and primary care settings, and in the home care environment. Raising awareness of concurrent FS in patients with HF patients and promoting targeted interventions may contribute to a decreased risk of adverse events, and a better prognosis and quality of life.

Keywords

Frailty, heart failure, older people, multidisciplinary care, assessment instruments, prognostic factors

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Correspondence: Izabella Uchmanowicz, Department of Clinical Nursing, Faculty of Health Science, Wrocław Medical University, Poland.

E: izabella.uchmanowicz@umed.wroc.pl

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The first paper that referred to the problem of ‘frail elderly patients’ was published in 1953, and frailty syndrome (FS) was first described in the 1990s.^{1,2} Although it has long been recognised and diagnosed, no consensus definition of this clinical syndrome has been established. The Second International Working Meeting on Frailty and Aging in 2006 concluded that FS involves increased vulnerability to external and internal stressors due to impairments in multiple interrelated physiological systems.^{3,4}

FS involves a lowering in reserves and decreased resistance to stressors. A simplified definition of FS concerns a loss of the body’s adaptive capabilities. From this perspective, FS is understood to be a process that dynamically accelerates ageing, but with no disability in its early stages. It is generally agreed that FS should be perceived as a multidimensional physical and psychological process associated with ageing.^{5,6,7}

In geriatric medicine, FS is defined as a state of increased vulnerability to endogenous and exogenous stress factors, resulting from decreased physiological reserves and dysfunction and dysregulation of multiple systems, which interfere with homeostasis and response to stress.^{8,9}

FS results in a higher risk of adverse events, including falls, disability and mortality. In this understanding, FS corresponds to an intermediate period between a state of unimpaired psychophysical functioning with full recovery capacity and a state of disability, impaired recovery, and transition from an anabolic to a more catabolic state.¹⁰

FS may be defined in two main ways: rule based or indicator based. Rule-based definitions include components used to evaluate individual patients. The best-known definition is that by Fried et al.; this comprises five frailty components: unintended body weight loss of 4.5 kg or more within the past year, low physical activity, slow walking speed, muscle weakness and subjectively reported exhaustion. However, it is not considered a gold standard as it may not reflect the multidimensional nature of frailty.^{1,2} Another method for defining and diagnosing FS involves ‘frailty indicators’, which are calculated by adding the number of deficits defined or by comparing the number of deficits found in a patient to the number of all deficits considered as part of frailty (diseases; cognitive, physical and functional dysfunctions; and abnormal laboratory results). This is associated with the notion of FS as an accumulation of deficits that impair one’s reserves and ability to respond to stressors.²

Potential definitions of FS are often synonymous with disability, multimorbidity or advanced old age.^{1,11} In geriatric medicine, FS is characterised as a biological syndrome associated with decreased reserves and resistance to stressors, resulting from an accumulation of deficits in multiple physiological systems, and causing vulnerability to adverse outcomes. FS is also likely to be associated with impairment of physiological processes or reserves in other systems, leading to a reduced capacity to maintain homeostasis when stressors are present, causing weaknesses.^{1,2,11,12} Nonetheless, 30% of the normal physiological reserves is considered a level sufficient to maintain adequate function of basic organs.¹³

With regard to homeostatic reserve decrease, three stages of frailty can be described: the initial process, the state of frailty and frailty-related complications.

The initial process is clinically silent. In this state, sufficient physiological reserves are maintained, the body reacts adequately to changes – such as acute disease, trauma or stress – and full recovery is possible.

The state of frailty can easily be diagnosed clinically. It includes slow and incomplete recovery after each subsequent incidence of acute disease, trauma or stress, which indicates that available reserves are insufficient for full recovery.

Progression of FS is associated with a high risk of frailty-associated complications, including falls, functional deficits leading to disability, polypharmacy, hospitalisation, cross-infection, institutionalisation and mortality.^{2,13} FS corresponds to an intermediate period between unimpaired psychophysical functioning with full recovery capacity and a state of disability with impaired ability to recover.¹²

Frailty Syndrome Pathophysiology

Most available scientific reports agree that FS involves increased vulnerability to biological stressors and its diagnosis should be based on an assessment of five criteria: slowness, weakness, physical activity, exhaustion and muscle mass.¹⁴

Unfortunately, it is often not easy to make a distinction between the clinical symptoms and signs related to ageing, chronic illness or frailty. It is even unclear whether frailty is an independent syndrome or a result of chronic illness or developing multiple comorbidities with ageing.¹⁵ Some authors show that frailty syndrome can be diagnosed in people who do not demonstrate any chronic illness.¹ Others argue that chronic illnesses and frailty share many characteristics, the most commonly cited example being heart failure (HF). Therefore, there is a link between FS and HF. HF is becoming a major challenge in cardiology, primarily owing to the rising prevalence because of ageing populations in developed countries. According to current estimates, by 2050, more than 40% of the population of western Europe will be 60 or older.¹⁶ A similar trend applies in Poland, where people aged 60 and above are expected to account for 35% of the population by the middle of this century.¹⁷

The incidence of FS increases with age, so the number of patients with concurrent FS and HF is anticipated to rise. Frailty is considered one of the most important issues associated with human ageing, and this has significant implications for patients and the healthcare system.¹ The relationship between frailty and a higher risk of falling, loss of functional independence, reduced quality of life, institutionalisation and mortality has been clearly demonstrated.^{18,19}

Both frail patients and those with HF may demonstrate poor tolerance of exertion, exhaustion and loss of body weight (muscle mass). Distinguishing frailty syndrome from heart failure may be particularly difficult in the elderly, who tend to show HF with preserved ejection fraction.¹⁴ Up to 25% of elderly patients with heart failure show frailty, and frail patients have an increased risk of developing heart failure.^{20–22} Frailty in chronic HF has been reported as possibly reversible in a study of patients undergoing heart transplantation or implantation of ventricular assist devices.²³

There seems to be a clear relationship between HF, ageing and frailty; however, this is poorly understood. All of the above-mentioned conditions are associated with elevated inflammatory markers, so a common inflammatory background has been proposed.¹⁵ This can be attributed to several mechanisms. A model of sterile inflammation has been proposed, where the breakdown of tissue (sterile cell necrosis without microbial invasion) connected with conditions such as ageing, MI and HF frees cellular substances, which in turn provokes a degree of immune response.²⁴ Such a mechanism seems to explain some of the common features of HF, ageing and frailty, because most of the signs and symptoms common in these conditions can be attributed to sarcopenia (loss of muscle mass). In this model, degradation of muscular tissue causes chronic, sterile inflammation.¹⁵

A chronic mild elevation of inflammatory markers in these conditions can be attributed to other mechanisms as well. It has been proposed that HF may lead to bacterial translocation as a result of intestinal hypoperfusion, and elevation of inflammatory markers in older patients may be caused by latent viral infections or the breaking down of both fatty and muscular tissue.¹⁵

Quality of life (QoL) is low in both the HF and the frail populations. Multimorbidity and physical, psychological and social frailty problems have been demonstrated to correlate negatively with QoL.^{25–27} It is generally accepted that almost half of the total population in Europe has at least one long-term condition. Among the most common chronic conditions in the European population are arthritis, diabetes, heart disease, cancer and stroke.²⁸ Many patients have two or more concurrent chronic diseases, especially those aged 65 years or older. Multimorbidity is associated with hospitalisation, emergency department visits and a reduction in QoL.^{12,13} It is more common in women than men.²⁸

Frailty Syndrome Epidemiology

Both frailty and HF are common in the elderly population. It is estimated that HF affects at least 26 million people worldwide.²⁹ The incidence of HF is associated with age – at 65 years, the estimated incidence of HF is 1% and this percentage approximately doubles with each decade of age thereafter.³⁰ Moreover, people aged 65 years or older constitute more than 80% of those with HF, and 25% of these patients are aged 80 years or older.³¹

Prevalence figures of frailty are highly dependent on the measurement instrument used. Roughly speaking, these instruments are based on the physical approach to frailty (physical frailty) or on the multidimensional approach to frailty (multidimensional frailty). Physical frailty instruments assess exclusively physical limitations that older people may have. An example is the phenotype of frailty by Fried, which includes unintentional weight loss, weakness, poor self-reported endurance, slow gait speed and low physical activity.¹

Multidimensional frailty instruments also include psychological and/or social components in their assessment. Examples include the Comprehensive Geriatric Assessment, the Frailty Index (FI) and the Tilburg Frailty Indicator (TFI).³²⁻³⁴ If frailty concerns only physical limitations that older people may have, its prevalence is generally lower than if it also covers psychological and social limitations. In community-dwelling older people aged 65 years or older, the prevalence of frailty varies enormously, and has been found to range from 4.0% to 59.1%.³⁵

Currently, no frailty instrument has been validated specifically for people with HF.³⁶ The most commonly used instrument is the phenotype of frailty, followed by the Comprehensive Geriatric Assessment and the FI.^{1,32,33} The use of these different instruments in people with HF explains why the prevalence figures of frailty in this target group also differ.

Denfeld et al. conducted a systematic review and meta-analysis that aimed to quantitatively synthesise studies about the prevalence of frailty in people with HF.³⁷ The overall prevalence of frailty in people with HF was found to be 44.5%. The authors also demonstrated that the prevalence of frailty was lower in studies using physical frailty than in those that also included psychological and/or social components of frailty, also called multidimensional frailty (42.9% versus 47.4%).³⁷

Many studies have shown that frailty is associated with older age.^{1,38,39} Altimir et al. found frailty occurred more often in people with HF aged 70 years or older, but even younger people with HF demonstrated a high prevalence of frailty (53.3% versus 33.3%).⁴⁰ Moreover, the prevalence of frailty was higher among women than among men (62.6% versus 33.7%). These findings were supported by Lupón et al.⁴¹

From the prevalence figures, it can be deduced that frailty and HF are closely linked. This is also evident from the results of two studies.^{22,42} The Longitudinal Aging Study Amsterdam (LASA) revealed that community-dwelling elderly people with HF had an increased risk of frailty, independent of potential confounders such as sex, age and multimorbidity.⁴² The Health ABC Study, which had a follow-up of 11.4 years and included 2,825 people with a mean age of 74 years at baseline, demonstrated that frailty is independently associated with risk of HF in older people.²²

Frailty is common in people with HF because the pathophysiology of HF contributes to frailty by reducing both skeletal muscle function and exercise capacity.⁴³ Frailty and HF are probably the result of similar pathways involving inflammatory processes as well as metabolic and autonomic disturbances.⁴⁴ In addition, the development of frailty in people with HF may be accelerated because they are more susceptible to falls and are more likely to have cognitive impairment because of reduced cerebral perfusion.⁴³ More major longitudinal studies are necessary to create clarity regarding the cause and effect relationship between frailty and HF.

Assessment Instruments for Frailty Syndrome

FS, rather than chronological age, is considered a significant risk factor for cardiovascular disease, and a significant predictor of outcomes. One important issue related to identifying frail patients is distinguishing between multimorbidity and/or disability and concurrent FS. Early FS identification offers an opportunity to provide individualised, targeted healthcare. Prevention of complications is a strategic health-related issue and should be prioritised in the process of evidence-based

therapeutic decision-making in elderly patients. Identification of frailty or early identification of pre-frailty may be significant in the prevention of FS consequences. FS diagnosis remains a challenge. Health and social care professionals have to choose the most suitable assessment instrument.⁴⁵ These are outlined below.

Edmonton Frail Scale

The Edmonton Frail Scale (EFS) comprises 10 domains evaluating cognitive function, balance, mobility, mood, independent daily functioning, medication, eating, health attitudes, social support and QoL. It should take less than 15 minutes to administer. The 'clock test' is used to assess cognitive function, and a walking test to evaluate balance and mobility. The maximum score is 17; scores of 0–3 indicate no frailty, and scores above 9 indicate the highest level of frailty.⁴⁶

Cardiovascular Health Study Scale

The Cardiovascular Health Study Scale (CHS) is one of the most commonly used frailty scales, and assesses its most important criteria.¹ These include:

- unintentional weight loss (>5 kg in 12 months);
- decreased grip strength, as measured using a dynamometer, taking the patient's age and body mass index (BMI) into consideration;
- exhaustion, as measured using a depression scale (CES–D, Center for Epidemiologic Studies Depression Scale);⁴⁷
- slow walking, that is, taking ≥ 20 seconds per 15 ft (approximately 4.6 m) in the walking test, considering the patient's age and sex;⁴⁸
- decreased physical activity, based on criteria from the short version of the Minnesota Leisure Time Activity Questionnaire (MLTAQ).⁴⁹

A positive result for three or more criteria corresponds to an FS diagnosis, while a score of 1 or 2 criteria indicates a predisposition to developing FS.¹

Tilburg Frailty Indicator

The TFI was developed by Gobbens et al.³⁴ Part A covers health-related determinants of frailty, while part B comprises 15 questions regarding the main FS components. The TFI includes three subscales, with eight physical, four psychological and three social components. There are no criteria for identifying high or low scores on each subscale, so results must be interpreted by comparing a patient's score with the maximum for each subscale. Moreover, each subscale includes a different number of questions, which also affects the interpretation.

The maximum score for the entire scale is 15 points. Frailty is identified when a patient scores 5 or more.⁵⁰

Canadian Study of Health and Aging Frailty Index

The Canadian Study of Health and Aging Frailty Index (CSHA-FI) was developed on the basis of a 5-year cohort study called the Canadian Study of Health and Aging. It included 10,262 respondents aged 65 and above.

The questionnaire covers deficits that interfere with daily functioning in elderly individuals, including:

- alarming symptoms: sleep disorders, memory impairment, low mood;
- physical signs, such as tremors and weakened pulse;

- laboratory results, including in particular abnormal creatinine and calcium levels;
- comorbidities, e.g. diabetes or Parkinson's disease;
- disability components, including limitations in activities of daily living such as washing, dressing, using the toilet and eating.

Depending on the results, each patient is categorised as: very fit, fit, managing well, vulnerable, mildly frail, moderately frail or severely frail.⁵¹⁻⁵³

FRAIL Scale

The FRAIL scale is a simple instrument recommended by the International Association of Nutrition and Aging. It is named for the five components it covers: Fatigue, Resistance, mobility (Aerobic), Illnesses, and Loss of weight. Notably, the score largely depends on the self-reported experience of the patient with regard to these components.⁵⁴

Groningen Frailty Indicator

The Groningen Frailty Indicator (GFI) questionnaire comprises 15 items concerning the severity of frailty symptoms, as well as limitations in daily functioning. Four main domains are identified: physical (mobility, health issues, fatigue, eyesight and hearing); psychological (mood disorders and depression symptoms); social (emotional isolation); and cognitive (cognitive functioning). FS is identified when a patient scores 4 or more.^{55,56}

MacArthur Study of Successful Aging Scale

This MacArthur Study of Successful Aging Scale (MSSA) is a modification of the CHS, with five added components. Besides the criteria covered by the CHS, it includes raised C-reactive protein (CRP) levels; increased interleukin 6 (IL-6) levels; decreased appetite identified using the Hopkins Symptom Checklist (HSCL); self-reported weakness identified using the same questionnaire; and cognitive impairment identified using tests for language skills, executive functions, spatial functions, and verbal and non-verbal memory. A positive result for at least 4 out of 10 components warrants a diagnosis of FS.⁵⁷

Calgary Cardiac and Cognition Scale

The questionnaire covers five key frailty indicators: cognitive impairment assessed using the Trail-Making Test; mood disorders identified using the Geriatric Depression Scale developed by Yesavage et al.; maintaining balance for less than 10 seconds in the Tandem Balance Test; a BMI <21 or >30 kg/m²; and living alone.⁵⁸⁻⁶¹ A positive result for three or more criteria is indicative of FS.⁵⁸⁻⁵⁹

Prognostic Role of Frailty in Heart Failure

The clinical consequences of concurrent frailty in patients with HF can vary, depending on the severity of both FS and HF. FS is often associated with limiting physical activity to the basic activities of daily living, such as washing or dressing, which may mask HF symptoms, as the latter are typically exacerbated by effort. The distortion of HF symptom severity by FS results in later diagnosis, and late (often too late) implementation of treatment.

Problems in self-care and difficulties in leaving home may reduce a patient's access to healthcare, which also contributes to insufficient treatment surveillance, delayed responses and untimely treatment modifications.

Patients with concurrent FS and HF require an individualised management approach, with particular focus on non-pharmaceutical treatment,

including psychological and social care. The difference between the two main approaches to FS is that one defines frailty as a physical phenotype, and the other considers frailty as a more multidimensional concept, concerning physical as well as psychological and social functioning.¹ These two different approaches are also reflected in the instruments developed for assessing frailty, and in the multidisciplinary approach, in which the therapeutic options considered do not include only medical interventions. Psychological and social support seems key in patients who are frail.

As FS very often affects elderly, cognitively impaired patients with multimorbidities who experience difficulties in self-care, management may be challenging. Patients with HF and concurrent FS require more attention than those without FS. As FS is estimated to affect as many as 70% or more of patients with HF aged 80 and above, the problem seems significant.⁶²

Weight loss is a major component of FS.⁶³⁻⁶⁵ Calorie supplementation helps weight gain and reduces complications and mortality in undernourished older individuals.⁶⁶ HF is often associated with eating disorders and a reduction in skeletal muscle, which may result in cachexia. Under its current definition, cachexia involves an unintended body weight loss (without changes in volemia) greater than 5% within 12 months (or a BMI <20 kg/m²), with at least three of the following criteria: decreased muscle strength; fatigue; anorexia; low fat-free mass index; and abnormal blood test results, including increased inflammatory markers (C-reactive protein, interleukin 6), anaemia (red blood cells <12 g/dl) or low albumin (<3.2 g/dl).⁶⁷ Cachexia is a generalised process affecting most tissues, including lean tissue such as skeletal muscle, fat tissue (energy reserves) and bone tissue (leading to osteoporosis). It may occur in 5–15% of patients with HF, especially those at more advanced stages of HF with reduced ejection fraction.⁶⁸

HF is also often associated with calcium–phosphorus imbalances resulting from secondary hyperparathyroidism and vitamin D deficiency, primarily caused by kidney dysfunction. Additionally, increased TNF- α in patients with HF suppresses calcitriol and vitamin D synthesis, and the resulting decrease in vitamin D concentration leads to a greater release of renin, which may accelerate the development of cachexia. Therefore, vitamin D supplementation is increasingly promoted in HF treatment. Research demonstrates that, besides increasing vitamin D concentration, the supplementation also decreases excess aldosterone in patients with HF.⁶⁹⁻⁷¹

Planned exercise should be a part of daily routine in all patients with HF and FS. The importance of physical activity in the management of a number of chronic diseases, including chronic HF or cancers, is currently under discussion.⁷² Exercise is a crucial part of FS management. It has been demonstrated that a year of resistance exercise in frail patients following hip fracture decreases hospitalisations and nursing home placement, and that 45–60 minutes of exercise three times a week seems to have positive effects on frail older adults and may be used for the management of frailty.^{73,74} Exercise in frail individuals increases their functional performance, walking speed, sit-to-stand test, stair climbing and balance, and decreases depression and fear of falling.⁷⁵

Individualisation seems essential in care for HF and FS patients. This means that healthcare professionals should focus their interventions on all three domains of human functioning – physical, psychological and social. The focus should be on characteristics such as poor physical

health, a lack of social relations, a lack of social support, feeling down and being unable to cope with problems, as these issues – as well as frailty components and HF – have the biggest impact on QoL in the elderly.⁷⁴

Directions for Future Research

It is well known that frailty has many adverse outcomes in the general population of older people, including disability, institutionalisation, hospitalisation, lower QoL and premature death.^{1,52,76,77} Logically, frailty also has several negative consequences for people with heart failure. A recent systematic review and meta-analysis based on 20 studies showed that frailty, measured with a wide variety of scales (e.g. the phenotype of frailty by Fried et al., FI, Canadian Study of Health and Aging Clinical Frailty Scale) is a significant predictor of all-cause mortality and hospital readmissions in people with heart failure.^{1,33,52,78}

In addition, in people with advanced HF, the risk of all-cause mortality after undergoing a ventricular assist device (VAD) implantation was significantly higher in those with frailty than in non-frail people.⁷⁸ According to Jha et al., in people with advanced HF undergoing a left ventricular assist device (LVAD) implantation, a preoperative measurement of frailty can identify people with increased postoperative risk of death, prolonged length of hospitalisation and longer use of intensive care.⁷⁹

Moayedi et al. showed that, adjusted for B-type natriuretic peptide or peak oxygen consumption (VO_2), frailty identified using the phenotype of frailty was not associated with increased mortality in people with advanced HF.⁸⁰ However, Moayedi et al. also found that when peak VO_2 was stratified into two categories (≥ 12 ml/kg/min versus < 12 ml/kg/min), frailty was associated with a 72% higher risk of death in this group.⁸⁰ Of the individual phenotype of frailty components, low physical activity assessed with the Duke Activity Status Index was associated with the highest risk of death.^{81,82} A study by Martin-Sánchez et al. showed that the presence of physical frailty in people with moderate disability has an impact on 30-day mortality in people ≥ 65 years with acute decompensated HF attending an emergency department.⁸³

Besides premature death and hospital (re)admission, studies have also shown that frailty in people with HF is significantly associated with other adverse outcomes such as disability and poorer quality of life.^{84,85} Vidan et al. demonstrated in a sample of 450 non-dependent people aged 70 years or older hospitalised for HF that frailty is a strong predictor of disability; among the five frailty phenotype components, low physical activity, low gait speed and weakness were predictive for early disability.⁸⁵ Furthermore, frailty has a negative impact on health-related QoL in older people with a diagnosis of HF; this is reflected by strong negative correlations between the TFI and both the physical and mental component scales of the Short Form Medical Outcomes Study Survey.^{84,86}

Many of the aforementioned studies used a measure of physical frailty, but studies have also examined a multidimensional measurement of frailty, providing evidence for using a multidimensional measurement of frailty in people with HF. Jha et al. concluded that adding cognitive impairment to the assessment of physical frailty improved the identification of people with advanced HF referred for heart transplantation who are at high risk of premature death.⁸⁷ Moreover, the Observational study to assess and Predict the in-patient course, risk of Re-Admission and mortality for patients hospitalised for or with

Heart Failure (OPERA-HF) study of 671 patients hospitalised for HF with a mean age of 76 years, showed that psychosocial factors are strongly associated with unplanned recurrent readmissions as well as mortality.⁸⁸ In another study, Uchmanowicz et al. demonstrated that the social frailty components of the TFI (living alone, loneliness and a lack of social support) were associated with hospital readmissions in people with HF.⁸⁹

Pulignano et al. found that an intensive, hospital-based disease management programme (DMP) for people with HF attending an HF outpatient clinic was more effective for those with mild-to-moderate frailty.⁹⁰ The DMP improved outcomes (death, heart failure admissions and all-cause admissions) and decreased costs. According to this research group, a multidimensional measurement of frailty could be useful for an appropriate selection of a model of care.

Tjam et al. made a similar recommendation based on a study of long-term residents with HF using the Resident Assessment Instrument (RAI) 2.0, a comprehensive assessment system developed particularly for frail older people.⁹¹ This study showed that the RAI 2.0 is superior to the New York Heart Association functional classification in predicting mortality in frail older people with HF. Moreover, Lee et al. provided evidence that physical and psychological symptom profiles appear to be useful in identifying adults (mean age 57 years) with HF who are at the highest risk of adverse clinical outcomes (worse 1-year event-free survival, independent of prognosis based on objective clinical data concerning HF).⁹² Among a sample of 192,327 adult hospitalisations for HF, four distinct comorbidity profiles – common, lifestyle, renal and neurovascular – were associated with differences in the length of stay, the risk of death and cost.⁹³ Together with frailty profiles, these comorbidity profiles could be helpful in identifying people with HF who are at a high risk of adverse outcomes while in hospital.

Despite the poor prognosis of people with both HF and frailty, it is important to note that frailty can be reversed or improved in people with HF. For example, Maurer et al. showed that implantation of a LVAD decreased frailty, defined as having three or more of the frailty components identified by Fried et al., and these positive changes in frailty were associated with improvement in quality of life, using the Kansas City Cardiomyopathy Questionnaire.^{1,94,95}

The current literature consistently demonstrates the added prognostic value of frailty in people with HF, for mortality and hospitalisation in particular. According to Jermyn and Patel, the inclusion of frailty into HF algorithms is possibly the next advancement in the management of HF by allowing healthcare providers to make better-founded decisions as well as make efficient use of healthcare resources.⁹⁶

Conclusion

FS is a complex clinical syndrome commonly associated with both older age and chronic illness. The significance and characteristics of FS in HF are increasingly recognised. Elderly patients with HF are a distinct population, and are characterised by a large number of comorbidities.

Old age is a significant predictor of FS. Other determinants of FS include strength, mobility, energy/fatigue, physical activity, nutrition, polypharmacy and cognitive function.

Elderly HF patients are at a higher risk of developing FS, but a converse relationship also exists in that patients aged above 65 years

with multimorbidity are at a higher risk of developing HF.⁹⁷ Thus, FS and HF have a bidirectional association, believed to be caused by proinflammatory factor activation, metabolic dysfunction and hormone dysregulation. Moreover, FS symptoms are found in nearly half of all patients with HF.⁹⁸

A variety of unidimensional and multidimensional instruments are used in FS diagnosis.⁹⁹ Regardless of the model used, a diagnosis of FS is associated with adverse outcomes.^{82,85,97,100–102} Consequences of concurrent FS in HF patients include an increase in hospital admission, poorer prognosis, higher risk of disability and falls, cognitive impairment and decreased QoL. In addition, increased severity of FS symptoms is associated with a fourfold increase of rehospitalisation risk and an increase in 1-year mortality in HF patients.¹⁰⁰ Considering FS and its implications may be a decisive factor in the diagnosis and treatment process for patients with HF.^{22,103}

For multidisciplinary healthcare teams, managing frail patients with HF remains a challenge. The overall objective of any intervention should be to improve outcomes, decrease hospitalisation, improve QoL and provide continued care.¹⁰⁴

Clinical Implications

Accurate evaluation in patients with FS and HF allows for the implementation of an individualised healthcare programme to prevent the adverse consequences of FS. Therefore, a consistent, multidimensional evaluation is necessary. Multidisciplinary teams should focus on rapid diagnosis to identify the high-risk group of patients with HF and concurrent FS, as this may be a decisive factor in improving prognosis and QoL in these patients.

HF treatment remains a challenge, especially in patients with concurrent FS. Providing comprehensive specialist care to patients with HF and FS should be a priority, and diagnosis and treatment optimised.

Implementation of strategies for identifying FS in patients with HF may be decisive with regard to individualisation of treatment and care plans.

There is an urgent need for accurate risk estimation, including factors associated with FS, in patients with HF. Management of HF should include the implementation of interventions to prevent frailty, alleviate its symptoms and prevent or limit its consequences. This objective may be achieved only through skilful collaboration between all team members, with a multidimensional consideration of frail HF patients. ■

- Petit-Dutaillis D, Chavany J, Guiot G. Operative frailty of patients with chromophobe adenoma of abnormal symptomatology: prognostic value of homonymous lateral hemianopsia. *Presse Med* 1953;61:341–3. PMID: 13073975.
- Winograd C, Gerety B, Chung M, et al. Screening for frailty: criteria and predictors of outcomes. *J Am Geriatr Soc* 1991;39:778–84. https://doi.org/10.1111/j.1532-5415.1991.006492.
- Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010;58:681–7. https://doi.org/10.1111/j.1532-5415.2010.02764.x; PMID: 20345864.
- Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm – issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007;62:731–7. PMID: 17634320.
- Yeolekar ME, Sukumaran S. Frailty syndrome: a review. *J Assoc Physicians India* 2014;62:34–8. PMID: 26281478.
- Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011;27:1–15. https://doi.org/10.1016/j.cger.2010.08.009; PMID: 21093718.
- Rockwood K, Hubbard R. Frailty and the geriatrician. *Age Ageing* 2004; 33: 429–30. https://doi.org/10.1093/ageing/afh153; PMID: 15315912.
- Cohen HJ. In search of the underlying mechanism of frailty. *J Gerontol A Biol Sci Med Sci* 2000;55:M706–8. https://doi.org/10.1093/gerona/55.12.M706; PMID: 11129391.
- Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition – consensus conference project. *J Gerontol A Biol Sci Med Sci* 2013;68: 62–7. https://doi.org/10.1093/gerona/gls119; PMID: 22511289.
- Bernabei R, Martone AM, Vetrano DL, et al. Frailty, physical frailty, sarcopenia: a new conceptual model. *Stud Health Technol Inform* 2014;203:78–84. https://doi.org/10.3233/978-1-61499-425-1-78; PMID: 26630514.
- Rockwood K, Stadnyk N, MacKnight C, et al. A brief clinical instrument to classify frailty in elderly people. *Lancet* 1999;353:205–6. https://doi.org/10.1016/S0140-6736(98)04402-X; PMID: 9923878.
- Bortz II WM. A conceptual framework of frailty: a review. *J Gerontol A Biol Sci Med Sci* 2002;57:M283–8. https://doi.org/10.1093/gerona/57.5.M283; PMID: 11983721.
- Michel JP, Lang PO, Zekry D. The frailty process: update to the phenotype and preventive strategies. *Annales de Gerontologie* 2008;1:e1–7. https://doi.org/10.1684/age.2008.0001.
- Goldwater D, Altman NL. Frailty and heart failure. American College of Cardiology, 5 August 2016. Available at: https://www.acc.org/latest-in-cardiology/articles/2016/08/05/08/40/frailty-and-heart-failure (accessed 15 January 2019).
- Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? *Aging Cell* 2017;16:444–50. https://doi.org/10.1111/acel.12581; PMID: 28266167.
- Marchel M. [Patient with chronic heart failure – outpatient management]. *Przewodnik Lekarski* 2007;10:24–31 [in Polish].
- Jurek K, Dobrowolska B. Older people, ageing and old age in the light of some public opinion surveys in Poland. *Ann Soc Sci* 2017;9:7–25. https://doi.org/10.18290/rns.2017.45.2-1.
- Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;62:744–51. https://doi.org/10.1093/gerona/62.7.744. PMID: 17634322.
- Gale CR, Cooper C, Deary IJ, Aihie Sayer A. Psychological well-being and incident frailty in men and women: the English Longitudinal Study of Ageing. *Psychol Med* 2014;44:697–706. https://doi.org/10.1017/S0033291713001384; PMID: 23822897.
- Boxer RS, Wang Z, Walsh SJ, et al. The utility of the 6-minute walk test as a measure of frailty in older adults with heart failure. *Am J Geriatr Cardiol* 2008;17:7–12. https://doi.org/10.1111/j.1076-7460.2007.06457.x; PMID: 18174754.
- Dodson JA, Chaudhry SI. Geriatric conditions in heart failure. *Curr Cardiovasc Risk Rep* 2012;6:404–10. https://doi.org/10.1007/s12170-012-0259-8; PMID: 23997843.
- Khan H, Kalogeropoulos AP, Georgiopoulou VV, et al. Frailty and risk for heart failure in older adults: the health, aging, and body composition study. *Am Heart J* 2013;166:887–94. https://doi.org/10.1016/j.ahj.2013.07.032; PMID: 24176445.
- Jha SR, Hannu MK, Wilhelm K, et al. Reversibility of frailty in advanced heart failure patients listed for transplantation. *J Heart Lung Transplant* 2012;35:529. https://doi.org/10.1016/j.healun.2016.01.077.
- Shen H, Kreisel D, Goldstein DR. Processes of sterile inflammation. *J Immunol* 2013;191:2857–63. https://doi.org/10.1093/immunol.1301539; PMID: 24014880.
- Bilotta C, Bowling A, Casé A, et al. Dimensions and correlates of quality of life according to frailty status: a cross-sectional study on community-dwelling older adults referred to an outpatient geriatric service in Italy. *Health Qual Life Outcomes* 2010;8:56. https://doi.org/10.1186/1477-7525-8-56; PMID: 20529325.
- Fortin M, Lapointe L, Hudon C, et al. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004;2:51. https://doi.org/10.1186/1477-7525-2-51; PMID: 15380021.
- Nóbrega TC, Jaluol O, Machado AN, et al. Quality of life and multimorbidity of elderly outpatients. *Clinics (Sao Paulo)* 2009;64:45–50. https://doi.org/10.1590/S1807-59322009000100009; PMID: 19142551.
- Renne I, Gobbens RJ. Effects of frailty and chronic diseases on quality of life in Dutch community-dwelling older adults: a cross-sectional study. *Clin Interv Aging* 2018;13:325–34. https://doi.org/10.2147/CIA.S156116; PMID: 29520132.
- Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1233–33. https://doi.org/10.1016/j.jacc.2013.11.053; PMID: 24491689.
- Butrous H, Hummel SL. Heart failure in older adults. *Can J Cardiol* 2016;32:1140–7. https://doi.org/10.1016/j.cjca.2016.05.005; PMID: 27476982.
- Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6–245. https://doi.org/10.1161/CIR.0b013e31828124ad; PMID: 23239837.
- Rubenstein LZ, Siu AL, Wieland D. Comprehensive geriatric assessment: toward understanding its efficacy. *Aging (Milano)* 1989;1:87–98. https://doi.org/10.1007/BF03323881; PMID: 2488312.
- Mitnitski AB1, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;1:323–36. https://doi.org/10.1100/tsw.2001.58; PMID: 12806071.
- Gobbens RJ, van Assen MA, Luijckx KG, et al. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc* 2010;11:344–55. https://doi.org/10.1016/j.jamda.2009.11.003; PMID: 20511102.
- Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012;60:1487–92. https://doi.org/10.1111/j.1532-5415.2012.04054.x; PMID: 22881367.
- McDonagh J, Martin L, Ferguson C, et al. Frailty assessment instruments in heart failure: a systematic review. *Eur J Cardiovasc Nurs* 2018;17:23–35. https://doi.org/10.1177/1474515117708888.
- Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2017;236:283–9. https://doi.org/10.1016/j.ijcard.2017.01.153; PMID: 28215466.
- Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing* 2015;44:162–5. https://doi.org/10.1093/ageing/afu148; PMID: 25313241.
- Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010;58:681–7. https://doi.org/10.1111/j.1532-5415.2010.02764.x; PMID: 20345864.
- Altimir S, Lupón J, González B, et al. Sex and age differences in frailty in a heart failure population. *Eur J Heart Fail* 2005;7:798–802. https://doi.org/10.1016/j.ejheart.2004.09.015; PMID: 16087134.
- Lupón J, González B, Santa Eugenia S, et al. Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. *Rev Esp Cardiol* 2008;61:835–42. https://doi.org/10.1016/S1885-5857(08)60231-5; PMID: 18684366.
- Kleipool EE, Hoogendijk EO, Trappenburg MC, et al. Frailty in older adults with cardiovascular disease: cause, effect or both? *Aging Dis* 2018;9:489–97. https://doi.org/10.14336/AD.2017.1125; PMID: 29896436.
- Shimura K. Cardiac senescence, heart failure, and frailty: a triangle in elderly people. *Keio J Med* 2016;65:25–32. https://doi.org/10.2302/kjm.2015-0015-IR; PMID: 27170235.
- Uchmanowicz I, Loboz-Rudnicka M, Szeląg P, et al. Frailty in heart failure. *Curr Heart Fail Rep* 2014;11:266–73. https://doi.org/10.1007/s11897-014-0198-4; PMID: 24733407.
- Piejko L, Nawrat-Szołtyś A. [Frailty syndrome – a challenge in an aging population]. *Hygeia Public Health* 2016;51:329–34 [in Polish].
- Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006;35:526–9. https://doi.org/10.1093/ageing/afh041; PMID: 16757522.
- Orme JG, Reis J, Herz EJ. Factorial and discriminative validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol* 1986;42:28–33. https://doi.org/10.1002/1097-4679(198601)42:1<28::AID-JCLP2270420104>3.0.CO;2-T; PMID: 3950011.
- Podsiadło D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8. https://doi.org/10.1111/j.1532-5415.1991.

- tb01616.x; PMID: 1991946.
49. Taylor HL, Jacobs DR Jr, Schucker BA, et al. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978;31:741–55. [https://doi.org/10.1016/0021-9681\(78\)90058-9](https://doi.org/10.1016/0021-9681(78)90058-9); PMID: 748370.
 50. Gobbens RJ, Luijckx KG, Wijnen-Sponselee MT, Schols JM. Towards an integral conceptual model of frailty. *J Nutr Health Aging* 2010;14:175–81. <https://doi.org/10.1007/s12603-010-0045-6>; PMID: 20191249.
 51. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;1:323–36. <https://doi.org/10.1100/tsw.2001.58>; PMID: 12806071.
 52. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95. <https://doi.org/10.1503/cmaj.050051>; PMID: 16129869.
 53. Koller K, Rockwood K. Frailty in older adults: implications for endoflife care. *Cleve Clin J Med* 2013;80:168–74. <https://doi.org/10.3949/ccjm.80a.12100>; PMID: 23456467.
 54. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008;9:71–2. <https://doi.org/10.1016/j.jamda.2007.11.005>; PMID: 18261696.
 55. Stevernik N, Slaets JPL, Schuurmans H, van Lis M. Measuring frailty: development and testing the GFI (Groningen Frailty Indicator). *Gerontologist* 2001;41:236–7.
 56. Slaets JP. Vulnerability in the elderly: frailty. *Med Clin North Am* 2006;90:593–601. <https://doi.org/10.1016/j.mcna.2006.05.008>; PMID: 16843764.
 57. Sarkisian CA, Gruenewald TL, John Boscardin V, Seeman TE. Preliminary evidence for subdimensions of geriatric frailty: the MacArthur Study of Successful Aging. *J Am Geriatr Soc* 2008;56:2292–7. <https://doi.org/10.1111/j.1532-5415.2008.02041.x>; PMID: 19016933.
 58. Sánchez-Cubillo I, Perriñez JA, Adrover-Roig D, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuospatial abilities. *J Int Neuropsychol Soc* 2009;15:438–50. <https://doi.org/10.1017/S155617709090626>; PMID: 19402930.
 59. Talarowska M, Zboralski K, Mossakowska-Wójcik J, Galecki P. [Results of the Trail Making Test among patients suffering from depressive disorders and organic depressive disorders.] *Psychiatr Pol* 2012;XLVI:273–82 [in Polish].
 60. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;12:37–49. PMID: 7183759.
 61. Freiheit EA, Hogan DB, Eliasziw M, et al. Development of a frailty index for patients with coronary artery disease. *J Am Geriatr Soc* 2010;58:1526–31. <https://doi.org/10.1111/j.1532-5415.2010.02961.x>; PMID: 20633198.
 62. Butrous H, Hummel SL. Heart failure in older adults. *Can J Cardiol* 2016;32:1140–7. <https://doi.org/10.1249/MS.0000000000001274>; PMID: 27476982.
 63. Landi F, Laviano A, Cruz-Jentoft AJ. The anorexia of aging: is it a geriatric syndrome? *J Am Med Dir Assoc* 2010;11:53–6. <https://doi.org/10.1016/j.jamda.2009.09.003>; PMID: 20188310.
 64. Morley JE. Undernutrition: a major problem in nursing homes. *J Am Med Dir Assoc* 2011;12:243–6. <https://doi.org/10.1016/j.jamda.2011.02.013>; PMID: 21527163.
 65. Morley JE. Weight loss in older persons: New therapeutic approaches. *Curr Pharm Des* 2007;13:3637–47. <https://doi.org/10.2174/138161207782794149>; PMID: 18220800.
 66. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009;CD003288. <https://doi.org/10.1002/14651858.CD003288.pub3>; PMID: 19370584.
 67. Okoshi MP, Capalbo RV, Romeiro FG, Okoshi K. Cardiac cachexia: perspectives for prevention and treatment. *Arq Bras Cardiol* 2017;108:74–80. <https://doi.org/10.5935/abc.20160142>; PMID: 27812676.
 68. Von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers – update 2014. *J Cachexia Sarcopenia Muscle* 2014;5:261–3. <https://doi.org/10.1007/s13539-014-0164-8>; PMID: 25384990.
 69. Witham MD, Crichton LJ, Gillespie ND, et al. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: A randomized controlled trial. *Circ Heart Fail* 2010;3:195–201. <https://doi.org/10.1161/CIRCHEARTFAILURE.109.907899>; PMID: 20103775.
 70. Boxer RS, Kenny AM, Schmotzer BJ, et al. A randomized controlled trial of high dose vitamin D3 in patients with heart failure. *JACC Heart Fail* 2013;1:84–90. <https://doi.org/10.1016/j.jchf.2012.11.003>; PMID: 24614995.
 71. Sciatti E, Lombardi C, Ravera A, et al. Nutritional deficiency in patients with heart failure. *Nutrients* 2016;8:E442. <https://doi.org/10.3390/nu8070442>; PMID: 27455314.
 72. Kubota Y, Evenson KR, Maclellrose RF, et al. Physical activity and lifetime risk of cardiovascular disease and cancer. *Med Sci Sports Exerc* 2017;49:1599–605. <https://doi.org/10.1249/MS.0000000000001274>; PMID: 28350711.
 73. Singh NA, Quine S, Clemson LM, et al. Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized controlled trial. *J Am Med Dir Assoc* 2012;13:24–30. <https://doi.org/10.1016/j.jamda.2011.08.005>; PMID: 21944168.
 74. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res* 2011;2011:569194. <https://doi.org/10.4061/2011/569194>; PMID: 21584244.
 75. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;14:392–7. <https://doi.org/10.1016/j.jamda.2013.03.022>; PMID: 23764209.
 76. Gobbens RJ, van Assen MA. The prediction of ADL and IADL disability using six physical indicators of frailty: a longitudinal study in the Netherlands. *Curr Gerontol Geriatr Res* 2014;2014:358137. <https://doi.org/10.1155/2014/358137>; PMID: 24782894.
 77. Kojima G1, Iliffe S1, Jivraj S2, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016;70:716–21. <https://doi.org/10.1136/jech-2015-206717>; PMID: 26783304.
 78. Zhang Y, Yuan M, Gong M, et al. Frailty and clinical outcomes in heart failure: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2018;19:1003–8.e1. <https://doi.org/10.1016/j.jamda.2018.06.009>; PMID: 30076123.
 79. Jha SR1, Hannu MK, Newton PJ, et al. Reversibility of frailty after bridge-to-transplant ventricular assist device implantation or heart transplantation. *Transplant Direct* 2017;3:e167. <https://doi.org/10.1097/TXD.0000000000000690>; PMID: 28706970.
 80. Moayed Y, Duero Posada JG, Foroutan F, et al. The prognostic significance of frailty compared to peak oxygen consumption and B-type natriuretic peptide in patients with advanced heart failure. *Clin Transplant* 2018;32:e13158. <https://doi.org/10.1111/ctr.13158>; PMID: 29168222.
 81. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651–4. [https://doi.org/10.1016/0002-9149\(89\)90496-7](https://doi.org/10.1016/0002-9149(89)90496-7); PMID: 27822256.
 82. Butrous H, Hummel SL. Heart failure in older adults. *Can J Cardiol* 2016;32:1140–7. <https://doi.org/10.1016/j.cjca.2016.05.005>; PMID: 27476982.
 83. Martín-Sánchez FJ, Rodríguez-Adrada E, Vidan MT, et al. Impact of frailty and disability on 30-day mortality in older patients with acute heart failure. *Am J Cardiol* 2017;120:1151–7. <https://doi.org/10.1016/j.amjcard.2017.06.059>; PMID: 28826899.
 84. Uchmanowicz I, Gobbens RJ. The relationship between frailty, anxiety and depression, and health-related quality of life in elderly patients with heart failure. *Clin Interv Aging* 2015;10:1595–600. <https://doi.org/10.2147/CLIA.S90077>; PMID: 26491276.
 85. Vidán MT, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;18:869–75. <https://doi.org/10.1002/ejhf.518>; PMID: 27072307.
 86. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247–63. <https://doi.org/10.1097/00005650-199303000-00006>; PMID: 8450681.
 87. Jha SR, Hannu MK, Gore K. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. *J Heart Lung Transplant* 2016;35:1092–100. <https://doi.org/10.1016/j.healun.2016.04.008>; PMID: 27282417.
 88. Sokoreli I, Pauws SC, Steyerberg EW. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. *Eur J Heart Fail* 2018;20:689–96. <https://doi.org/10.1002/ejhf.1112>; PMID: 29314447.
 89. Uchmanowicz I, Kuśniercz M, Wleklek M, et al. Frailty syndrome and rehospitalizations in elderly heart failure patients. *Aging Clin Exp Res* 2018;30:617–23. <https://doi.org/10.1007/s40520-017-0824-6>; PMID: 28849550.
 90. Pulignano G, Del Sindaco D, Di Lenarda A, et al. Usefulness of frailty profile for targeting older heart failure patients in disease management programs: a cost-effectiveness, pilot study. *J Cardiovasc Med (Hagerstown)* 2010;11:739–47. <https://doi.org/10.2459/JCM.0b013e328339d981>; PMID: 20736784.
 91. Tjam EY, Heckman GA, Smith S. Predicting heart failure mortality in frail seniors: comparing the NYHA functional classification with the Resident Assessment Instrument (RAI) 2.0. *Int J Cardiol* 2012;155:75–80. <https://doi.org/10.1016/j.ijcard.2011.01.031>; PMID: 21292334.
 92. Lee CS, Gelow JM, Denfeld QE. Physical and psychological symptom profiling and event-free survival in adults with moderate to advanced heart failure. *J Cardiovasc Nurs* 2014;29:315–23. <https://doi.org/10.1097/JCN.0b013e3285968a>; PMID: 23416942.
 93. Lee CS, Chien CV, Bidwell JT. Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: an analysis of the US Nationwide inpatient sample. *BMC Cardiovasc Disord* 2014;14:73. <https://doi.org/10.1186/1471-2261-14-73>; PMID: 24898986.
 94. Maurer MS, Horn E, Reyentovich A. Can a left ventricular assist device in individuals with advanced systolic heart failure improve or reverse frailty? *J Am Geriatr Soc* 2017;65:2383–90. <https://doi.org/10.1111/jgs.15124>; PMID: 28940248.
 95. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;35:12–55. [https://doi.org/10.1016/S0735-1097\(00\)00531-3](https://doi.org/10.1016/S0735-1097(00)00531-3); PMID: 10758967.
 96. Jermyn R, Patel S. The biologic syndrome of frailty in heart failure. *Clin Med Insights Cardiol* 2015;8(Suppl 1):87–92. <https://doi.org/10.4137/CMC.S15720>; PMID: 25861225.
 97. Goldwater DS, Pinney SP. Frailty in advanced heart failure: a consequence of aging or a separate entity? *Clin Med Insights Cardiol* 2015;9:39–46. <https://doi.org/10.4137/CMC.S19698>; PMID: 26244037.
 98. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747–62. <https://doi.org/10.1016/j.jacc.2013.09.070>; PMID: 24291279.
 99. Goldfarb M, Sheppard R, Afilalo J. Prognostic and therapeutic implications of frailty in older adults with heart failure. *Curr Cardiol Rep* 2015;17:651. <https://doi.org/10.1007/s11886-015-0651-3>; PMID: 26346250.
 100. McNallan SM, Singh M, Chamberlain AM, et al. Frailty and healthcare utilization among patients with heart failure in the community. *JACC Heart Fail* 2013;1:135–41. <https://doi.org/10.1016/j.jchf.2013.01.002>; PMID: 2395695.
 101. Vidan MT, Sanchez E, Fernandez-Aviles F, et al. Frail-HF, a study to evaluate the clinical complexity of heart failure in nondependent older patients: rationale, methods and baseline characteristics. *Clin Cardiol* 2014;137:725–32. <https://doi.org/10.1002/clc.22345>; PMID: 25516357.
 102. Afilalo J, Karunananthan S, Eisenberg MJ, et al. Role of frailty in patients with cardiovascular disease. *Am J Cardiol* 2009;103:1616–21. <https://doi.org/10.1016/j.amjcard.2009.01.375>; PMID: 19463525.
 103. Kalogeropoulos A, Georgiopoulos V, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) Study. *J Am Coll Cardiol* 2010;55:2129–37. <https://doi.org/10.1016/j.jacc.2009.12.045>; PMID: 20445737.
 104. Piepoli MF, Davos C, Francis DP, et al. Exercise training metaanalysis of trials in patients with chronic heart failure (EXTRA-MATCH). *BMJ* 2004;328:189. <https://doi.org/10.1136/bmj.328.7441.111-b>; PMID: 14729656.