The Impact of Frailty and Comorbidities on Heart Failure Outcomes

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Abstract

Frailty is a multisystemic process leading to reduction of physiological reserve and a reduction in physical activity. Heart failure (HF) is recognised as a global cause of morbidity and mortality, increasing in prevalence over recent decades. Because of shared phenotypes and comorbidities, there is significant overlap and a bidirectional relationship, with frail patients being at increased risk of developing HF and vice versa. Despite this, frailty is not routinely assessed in patients with HF. Identification of these patients to direct multidisciplinary care is key, and the development of a frailty assessment tool validated in a large HF population is also an unmet need that would be of considerable benefit in directing multidisciplinary-team management. Non-pharmacological treatment should be included, as exercise and physical rehabilitation programmes offer dual benefit in frail HF patients, by treating both conditions simultaneously. The evidence for nutritional supplementation is mixed, but there is evidence that a personalised approach to nutritional support in frail HF patients can improve outcomes.

Keywords

Frailty, heart failure, comorbidity

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The word frail originates from the French word *frêle*, meaning 'of little resistance', and from the Latin word *fragilis*, meaning 'easily broken'. In clinical medicine, frailty is considered one of the significant debilitating medical syndromes commonly associated with ageing and chronic disease that implies a multifactorial decrease in physiological reserve to withstand biological stressors.[1] Frailty is thought to be caused by multisystem dysregulations, chronic inflammation, cachexia and sarcopenia, resulting in an increased risk of morbidity and mortality.[2]

It is estimated that in the UK, the prevalence of frailty in the general population is 8.5% in women and 4.1% in men.[3] In the diseased state, mortality risk generally increases with age.[4] However, this risk is not uniform and the concept of frailty can be used to describe the heterogeneity of increased risk in people of the same age.[5] Frailty is also important in explaining some of the differences in disease presentation. For example, in a fit individual, a heart attack commonly presents with classic cardiac chest pain, while in the frail individual this presentation is less common and being generally unwell or newly confused is more frequent.[6]

Heart failure (HF) is a global cause of morbidity and mortality with an estimated 5.7 million cases in the US alone.[7] There is substantial and rapidly growing interest at the intersection between frailty and HF, as it has been shown that frailty is a powerful marker of poor prognosis and marker of outcome in the HF population.[8–11] Indeed, there exists significant phenotypic and symptomatic overlap between both conditions (*Figure 1*). Furthermore, up to 44.5% of HF patients were considered frail using contemporary measures in a 2017 meta-analysis.[12] This is independent of age or New York Heart Association classification.[13] The significant bidirectional relationship between frailty and HF is evidenced by the fact that HF patients are 600% more likely to be frail and patients with frailty have a significant increased risk of developing HF.[14,15] Furthermore, patients with both conditions are often more complex and have a greater burden of other comorbidities including – but not limited to – chronic obstructive pulmonary disease, chronic kidney disease, dementia and anaemia.[1,11,16]

Interestingly, frailty appears to be much more common in HF with preserved ejection fraction (HFpEF) than in HF with reduced ejection fraction (HFrEF).[17] This is likely to be secondary to the fact that HFpEF patients typically suffer a great burden of comorbidities compared to the HFrEF population.[17] Furthermore, HFpEF patients are more likely to suffer non-cardiac hospitalisations.[17] Finally, frailty is more likely to be present in those who present to hospital with acute decompensation than in well-compensated community HF patients.[18]

The focus of this article is to review the literature with regards to HF and frailty. Specifically, this article will focus on the pathophysiology of frailty, its assessment in HF and its prognostic implications.

Figure 1: Overlap Between Frailty and Heart Failure

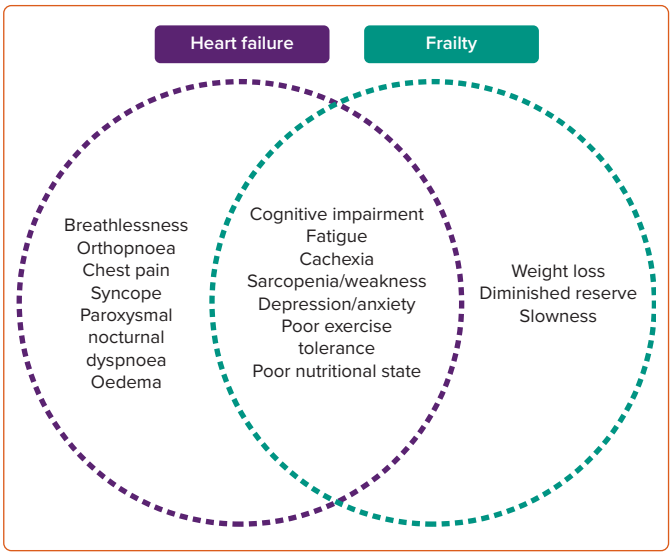
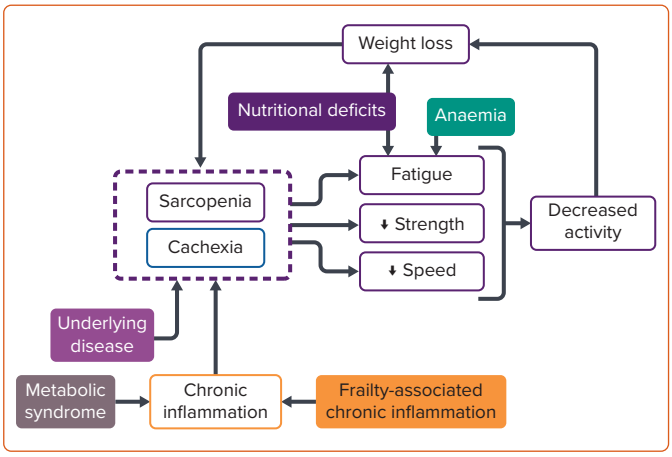


Figure 2: Processes Involved in the Development of Frailty



Pathophysiology of Frailty

The physiological processes involved in the development of frailty syndrome are predominantly of an immune, endocrine and musculoskeletal nature resulting in a reduction in strength, endurance or cognitive function (*Figure 2*).[19–21]

Inflammatory pathways have been elucidated as an important mechanism in the development of frailty syndrome.[22,23] Population-based studies have linked elevated levels of the proinflammatory cytokine interleukin-6 to frailty in both community and inpatient populations in addition to identifying higher serum levels of C-reactive protein, tissue necrosis factor-α, and white blood cells in frail members of community and inpatient populations aged ≥70 years.[22,24,25] Additionally, lower levels of the negative acute phase reactant albumin correlate with a higher degree of frailty in inpatients aged >75 years.[22]

Nutritional deficits have also been implicated in the pathophysiology of frailty, with frail patients more likely to have multiple nutritional deficits than non-frail patients.[25] High protein intake appears to be protective against frailty in older populations and, conversely, low protein intake has been associated with higher frailty risk.[26,27] Micronutrient deficits are also associated with frailty risk, with low intake of vitamins D, E and C, and folate being associated with frailty independent of total calorie intake.[26] Vitamin B_{12} deficiency has also been identified as more common in pre-frail or frail individuals when compared with a non-frail population.[28] Healthier diets, such as the Mediterranean diet and high fruit and vegetable intakes, have been associated with decreased risk of frailty in meta-analyses.[29,30]

Finally, the development of anaemia has been identified as a contributing factor to frailty syndrome. Anaemia is more prevalent amongst frail populations and haemoglobin levels negatively correlate with frailty risk.[31–33] The anaemia identified in frail patients is commonly found to be normocytic, with haemoglobin levels inversely correlated with interleukin-6, suggesting an interplay between anaemic and inflammatory pathological processes in the development of frailty syndrome.[32]

Once established, the phenotypical characteristics of frailty feed into each other, leading to a downward spiral in which the patient is perpetually becoming increasingly frail. Key to this cycle are the processes of sarcopenia and cachexia. These conditions often overlap but have distinct definitions. Sarcopenia is typically defined by low muscle mass and function, while cachexia is defined as weight loss in the presence of underlying illness, with chronic inflammation identified as a key pathophysiological mechanism.[34,35] Considering the prevalence of markers of chronic inflammation seen in frailty patients, it can be assumed that cachexia plays a role in the pathological cycle amongst a significant proportion of patients with frailty. *Figure 1* illustrates the role of abnormal physiology in the cycle of frailty progression, with reference to Fried's cycle of frailty.[36]

Identifying Frailty in Heart Failure

The assessment of frailty in the HF patient is challenging because of the lack of a universal, easily used set of diagnostic criteria or screening tool. While the term 'frailty syndrome' was first described in 1991 in a landmark paper,and has since been adopted into clinical practice and the research environment, as of 2021, there is still no internationally agreed definition or diagnostic criteria.[37] Furthermore, frailty is widely recognised and used by the general clinician in guiding treatment decisions and estimating prognosis. This recognition is often performed using a superficial 'eyeball test' or the 'end-of-the-bed-o-gram' rather than a validated frailty risk assessment. This is because the most well-validated tools can often be cumbersome and resource-intensive in routine medical practice.

Generally, frailty assessment tools are derived from two basic concepts in frailty: a unidimensional/physical model that views frailty as a physical problem, and a multidimensional/holistic model that incorporates both physical problems as well as psychological and social problems.[38,39] In a recent review, 67 frailty measurement instruments were identified, and these often-exhibited significant heterogeneity with regards to which parameters were used.[40] *Table 1* shows the nine most cited frailty assessment tools identified from this review and their individual constituents.[40]

The frail phenotype/Fried scale is the single most commonly used and validated tool in the cardiovascular disease (CVD) population.[36] This was first described over two decades ago and subsequently validated in the in the Women's Health and Aging study.[36,40] The Fried scale consists of five domains: unintentional weight loss, weakness as measured by hand grip strength, self-reported exhaustion, a slow gait speed and low self-reported physical activity. Frailty is defined as three or more criteria being present, and pre-frailty as two or more. The presence of frailty as

Table 1: Most Cited Frailty Assessment Instruments and Their Constituents

	Frail Phenotype (2001)[36]	Deficient Accumulation Frailty Index (2001)[40]	Gill Frailty Measure (2002)[86]	Clinical Frailty Scale (2005)[87]	Brief Frailty Instrument (1999)[88]	Vulnerable Elders Survey (2001)[89]	Frail Scale (2008)[90]	Winograd Screen Instrument (1991)[37]
Physical activity	+	+	+	+	+	+	+	+
Mobility	+			+			+	
Energy	+			+			+	+
Cognition		+		+	+			+
Social aspect		+		+				
Disability				+		+		
Medication				+				
Health						+		+
Nutrition	+							+
Strength	+					+		+
Comorbidity		+					+	
Continence					+			+
Weight loss							+	+

measured on the Fried scale has been demonstrated with worse clinical outcomes and a greater functional impairment in both the HF and non-HF population.[41,42] Fried's criteria is the most used tool to measure frailty, but it can be limited by capturing only the physical frailty, and the requirement for a dynamometer precludes its use without special equipment. Finally, in the context of diuresis it is difficult to accurately assess unintentional weight loss.

The deficient accumulation frailty index is another commonly used frailty tool often used in the CVD population.[43] It sums the total number of impairments a patient has during their activities of daily living, comorbid conditions, and abnormal laboratory values. Frailty index categorises the individuals in a quantitative continuum rather than an absolute and can often be assessed from medical records. The disadvantages of this assessment tool are that it is time consuming in routine use and its reliance of the number of deficits rather than the nature of the deficit. Therefore, in certain circumstances it may overestimate the frailty burden.

While a variety of frailty measures and scores have been used in HF, none have been developed and validated in this cohort. These patients are more difficult to assess using contemporary frailty scores for multiple reasons including, but not limited to, the significant overlap between frailty and HF, and the inference of frailty with possible HF treatment. The need for a HF frailty assessment tool prompted the Heart Failure Association of the European Society of Cardiology (ESC) to release a position paper in 2019 on frailty in HF, defining frailty and creating a foundation (based on clinical, psycho-cognitive, functional, and social domains) for the design of a tailored validated score in the HF patient.[44,45]

Prognostic Implications of Frailty in Heart Failure Patients

While there is no single validated frailty assessment tool in the HF population, there is still considerable evidence demonstrating that frailty and its components are correlated with worse HF outcomes. Hand grip strength has consistently been found to be an independent predictor of survival in the HF population, with higher grip strength corresponding with increased survival.[46] In a meta-analysis in >2,300 patients with CVD including HF, lower hand grip strength was associated with increased risk of CVD death, all-cause mortality, and admission for HF.[47] Poor lower-extremity function at baseline, measured by gait speed or functional assessments such as the 6-minute walk test (6MWT) or the short physical performance battery, has also been associated with increased all-cause and HF mortality.[48,49]

Additionally, HF patients with decreased gait speed or poorer lower extremity function at follow-up are at higher risk of all-cause mortality when compared with HF patients who maintain gait speed or lower extremity function.[48] Higher gait speed or better lower-extremity performance at baseline have also been demonstrated to reliably predict a lower risk of all cause and HF hospitalisation, with improvement in lower-extremity performance or gait speed at follow up reducing risk of all-cause hospitalisation further.[48,50,51] Self-reported exhaustion/fatigue is an important component of the frailty phenotype. Fatigue is more challenging to measure objectively, therefore research into its relationship with HF is more limited. However, it has been demonstrated that greater levels of fatigue are linked with worse clinical outcomes after controlling for other prognostic variables.[52] Cognitive impairment is a commonly cited feature on many frailty assessment scales and is more prevalent in the HF population, and has been associated with increased hospitalisation in HF patients.[53,54]

Despite the perceived issues with identifying an existing frailty assessment tool for use in estimating HF prognosis, there have been efforts to validate existing frailty assessments tools for this purpose. Boxer et al. categorised 60 HF patients into three groups based on the frailty phenotype status where the frail patients had the highest mortality at follow-up compared to their counterparts.[55] Similarly, in the study by Madan et al. in 40 HF patients, frailty was associated with increased combined endpoint of mortality and all-cause hospitalisation.[56] McNallan et al. investigated the relationship between frailty and mortality in HF patients using a the deficit model and a modified version of Fried's frailty phenotype, differing in patient assessment by using the physical component score of the Short Form 12 health questionnaire as a surrogate for both strength and speed.[57,58] This demonstrated that in HF patients defined as frail, the risk of mortality was doubled (HR 2.04; 95% CI [0.99–4.18]). Tanaka et al.

demonstrated that frailty is independently associated with worse clinical outcomes irrespective of age, BMI, ejection fraction and gender.[59]

In the advanced HF population awaiting a heart transplant, frailty was found to be an independent predictor of all-cause mortality.[60] Furthermore, this finding was replicated in patients with HF following CRT with the implication that frailty is an independent predicator of response to CRT.[61] In the left ventricular assist device (LVAD) population HF has repeatedly been demonstrated to independently predict outcomes.[62,63] Furthermore, in patients with sarcopenia undergoing LVAD therapy, there was a general trend towards increasing hospital stay and mortality.[64]

In summary, there is significant evidence that both the individual components of frailty and various definitions of frailty as a syndrome can be used to predict prognosis in HF patients.

Management Implications in the Frail Heart Failure Patient

Frailty adds an increasing layer of complexity to the management of the already complex HF patient. Frailty also leaves patients more at risk from guideline-directed medical therapy because of their increased vulnerability to adverse drug effects, such as hypotension and subsequent falls. Therefore, the management of the frail HF patient involves more pragmatism and less rigorous adherence to guidelines. Furthermore, frail patients are more likely to benefit from non-pharmacological interventions than their non-frail counterparts. There are currently two broad categories of intervention for the frail HF patient: exercise and physical rehabilitation and diet and nutritional strategies.

Exercise and Physical Rehabilitation

The 2021 ESC HF guidelines suggest that supervised, exercise-based cardiac rehabilitation programmes should be offered to patients who are frail or with multiple comorbidities. This is based on a class IIa level of evidence.[65] Exercise programmes are a promising intervention in frail HF patients as there is evidence of dual benefit, addressing both a patient's cardiac failure and frailty simultaneously. For HF patients, the positive impact of exercise on physical function, quality of life and exercise capacity is well documented.[66–68] Despite these benefits, uncertainty still exits regarding the overall impact on mortality and HF hospitalisations.[69,70] Intense exercise therapy has shown that it may improve peak oxygen consumption (VO_2).[71] Furthermore, exercise training has been shown to reduce serum markers of inflammation in HF patients, suggesting a reduction in the chronic inflammation that acts as a key pathophysiological process in both HF and frailty.[72,73] Inflammation may also play a role in predicting benefit from exercise training, as HF patients with higher baseline levels of inflammatory biomarkers have been noted to show poorer improvements in peak VO_2 as a result of exercise training when compared with HF patients with lower baseline inflammatory biomarkers.[74]

Diet and Nutrition Strategies

Dietary support in frailty aims to address the numerous nutritional deficits seen in frail patients. Micronutrient deficiencies common in frailty include vitamins D, E, A, B_{12}, thiamine, iron and folate.[75] Long-term vitamin D supplementation in the advanced HF patient has not been demonstrated to reliably improve outcomes or cause harm.[76] Thiamine supplementation has been found to be ineffectual in impacting HF progression or physical performance, and while folate supplementation has shown promise in lowering N-terminal pro-brain natriuretic peptide levels, the evidence for this is limited and there is no evidence of clinical benefit in HF populations.[77,78] The evidence for micronutrient supplementation (calcium, magnesium, zinc, copper, selenium, thiamine, riboflavin, folate, vitamins A, B6, B12, C, E, D and coenzyme Q10) is mixed and inconclusive.[79,80] Iron replacement in the frail HF patient has a strong evidence base and patients should be regularly screened and treated.[65]

With regards to macronutrients, high-calorie, high-protein diets in HF patients with significant unintended weight loss have been demonstrated to improve quality of life and 6MWT performance.[81] Supplementation with essential amino acids has been shown to improve peak VO_2 and 6MWT performance in muscle-depleted HF patients but did not increase muscle mass.[82] Conversely, supplementing resistance exercise with branched chain amino acids in HF patients led to no additional improvement in strength or VO_2 max when compared with HF patients undertaking exercise without supplementation.[83]

The future of nutritional support in frail HF patients may lie in a patient-personalised approach. In a clinical trial of 120 malnourished patients hospitalised with HF, personalised nutritional interventions delivered over a 6-month period led to decreased all-cause mortality (20.3% versus 47.5%; HR 0.37; 95% CI [0.19–0.72]; p=0.003), cardiovascular mortality (16.9% versus 42.6%; HR 0.35; 95% CI [0.17–0.72]; p=0.004) and re-admission for HF (10.2 versus 36.1%; HR 0.21; 95% CI [0.09–0.52]; p=0.001).[84] Taken together, this suggests that nutritional treatments of frailty in HF should be tailored to the individual patient's nutritional needs, with or without micronutrient supplementation where appropriate. Further research is required to assess the impact of personalised nutritional support in non-malnourished frail HF patients.

The Role of the Multispecialty Multidisciplinary Team in Heart Failure Management

Recent evidence from Liverpool, UK, has shown that a multispecialty multidisciplinary team approach provides seamless integration of primary care community services with secondary and tertiary care.[85] The multispecialty team consists of HF specialists (consultants, specialist nurses), along with a geriatrician, renal physician, diabetes specialist, chest physician, pharmacist, pharmacologist and palliative care physician. This approach allows for consensus decisions from multidisciplinary team meetings, providing a holistic approach for HF patients with comorbidities, polypharmacy and frailty. This approach can also reduce hospitalisations and inconvenience to patients by preventing the need to attend multiple specialty clinics. This model can also lead to significant cost savings to the healthcare system.

Conclusion

HF is among the high-priority challenges in the field of cardiology. Frailty represents the endpoint of a multitude of complex processes. The incidence of frailty and HF and the combination of both is increasing with an ageing population. The frail HF patient represents the most complex presentation of HF.

Routine and meaningful assessment and management of frailty in the HF patient can offer more intensive treatment to improve outcomes. These patients are likely to be more complex than their non-frail counterparts and more likely to benefit from a multidisciplinary HF team approach. Physical exercise programmes are a useful resource and are recognised in ESC HF guidelines. Further research on personalised nutritional interventions in frail HF patients is recommended to validate the promising evidence available at present. Finally, development and validation of an assessment tool to identify frailty in HF populations is recommended to facilitate delivery of multidisciplinary care to these complex patients. ❑

1. Cesari M, Calvani R, Marzetti E. Frailty in older persons. *Clin Geriatr Med* 2017;33:293–303. https://doi.org/10.1016/j.cger.2017.02.002; PMID: 28689563.
2. Fedarko NS. The biology of aging and frailty. *Clin Geriatr Med* 2011;27:27–37. https://doi.org/10.1016/j.cger.2010.08.006; PMID: 21093720.
3. Syddall H, Roberts HC, Evandrou M, et al. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. *Age Ageing* 2010;39:197–203. https://doi.org/10.1093/ageing/afp204; PMID: 20007127.
4. Vaupel JW, Carey JR, Christensen K, et al. Biodemographic trajectories of longevity. *Science* 1998;280:855–60. https://doi.org/10.1126/science.280.5365.855; PMID: 9599158.
5. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography* 1979;16:439–54. https://doi.org/10.2307/2061224; PMID: 510638.
6. Saunderson CE, Brogan RA, Simms AD, et al. Acute coronary syndrome management in older adults: guidelines, temporal changes and challenges. *Age Ageing* 2014;43:450–5. https://doi.org/10.1093/ageing/afu034; PMID: 24742588.
7. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;6:606–19. https://doi.org/10.1161/HHF.0b013e318291329a; PMID: 23616602.
8. 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: 23956958.
9. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest* 2005;35:723–30. https://doi.org/10.1111/j.1365-2362.2005.01572.x; PMID: 16313247.
10. Uchmanowicz I, Łoboz-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.
11. Uchmanowicz I, Młynarska A, Lisiak M, et al. Heart failure and problems with frailty syndrome: Why it is time to care about frailty syndrome in heart failure. *Card Fail Rev* 2019;5:37–43. https://doi.org/10.15420/cfr.2018.37.1; PMID: 30847244.
12. 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;236:283–89. https://doi.org/10.1016/j.ijcard.2017.01.153; PMID: 28215466.
13. Newman AB, Gottdiener JS, Mcburnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001;56:M158–66. https://doi.org/10.1093/gerona/56.3.M158; PMID: 11253157.
14. 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.
15. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc* 2005;53:1321–30. https://doi.org/10.1111/j.1532-5415.2005.53405.x; PMID: 16078957.
16. Uchmanowicz I, Lisiak M, Wontor R, et al. Frailty syndrome in cardiovascular disease: clinical significance and research tools. *Eur J Cardiovasc Nurs* 2015;14:303–9. https://doi.org/10.1177/1474515114568059; PMID: 25595359.
17. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012;59:998–1005. https://doi.org/10.1016/j.jacc.2011.11.040; PMID: 22402071.
18. Reeves GR, Whellan DJ, Patel MJ, et al. Comparison of frequency of frailty and severely impaired physical function in patients ≥60 years hospitalized with acute decompensated heart failure versus chronic stable heart failure with reduced and preserved left ventricular ejection fraction. *Am J Cardiol* 2016;117:1953–8. https://doi.org/10.1016/j.amjcard.2016.03.046; PMID: 27156830.
19. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014;9:433–41. https://doi.org/10.2147/CIA.S45300; PMID: 24672230.
20. 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.
21. Sternberg SA, Wershof Schwartz A, Karunananthan S, et al. The identification of frailty: a systematic literature review. *J Am Geriatr Soc* 2011;59:2129–38. https://doi.org/10.1111/j.1532-5415.2011.03597.x; PMID: 22091630.
22. Hubbard RE, O'Mahony MS, Savva GM, et al. Inflammation and frailty measures in older people. *J Cell Mol Med* 2009;13:3103–9. https://doi.org/10.1111/j.1582-4934.2009.00733.x; PMID: 19438806.
23. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev* 2016;31:1–8. https://doi.org/10.1016/j.arr.2016.08.006; PMID: 27592340.
24. Leng SX, Xue QL, Tian J, et al. Inflammation and frailty in older women. *J Am Geriatr Soc* 2007;55:864–71. https://doi.org/10.1111/j.1532-5415.2007.01186.x; PMID: 17537086.
25. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci* 2009;64:1049–57. https://doi.org/10.1093/gerona/glp076; PMID: 19567825.
26. Bartali B, Frongillo EA, Bandinelli S, et al. Low nutrient intake is an essential component of frailty in older persons. *J Gerontol A Biol Sci Med Sci* 2006;61:589–93. https://doi.org/10.1093/gerona/61.6.589; PMID: 16799141.
27. Coelho-Júnior HJ, Rodrigues B, Uchida M, et al. Low protein intake is associated with frailty in older adults: a systematic review and meta-analysis of observational studies. *Nutrients* 2018;10:1334. https://doi.org/10.3390/nu10091334; PMID: 30235893.
28. Matteini AM, Walston JD, Fallin MD, et al. Markers of B-vitamin deficiency and frailty in older women. *J Nutr Health Aging* 2008;12:303–8. https://doi.org/10.1007/BF02982659; PMID: 18443711.
29. Rashidi Pour Fard N, Amirabdollahian F, Haghighatdoost F. Dietary patterns and frailty: a systematic review and meta-analysis. *Nutr Rev* 2019;77:498–513. https://doi.org/10.1093/nutrit/nuz007; PMID: 31038679.
30. Ghoreishy SM, Asoudeh F, Jayedi A, et al. Fruit and vegetable intake and risk of frailty: a systematic review and dose response meta-analysis. *Ageing Res Rev* 2021;71:101460. https://doi.org/10.1016/j.arr.2021.101460; PMID: 34534684.
31. Palmer K, Vetrano DL, Marengoni A, et al. The relationship between anaemia and frailty: a systematic review and meta-analysis of observational studies. *J Nutr Health Aging* 2018;22:965–74. https://doi.org/10.1007/s12603-018-1049-x; PMID: 30272101.
32. Leng S, Chaves P, Koenig K, et al. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc* 2002;50:1268–71. https://doi.org/10.1046/j.1532-5415.2002.50315.x; PMID: 12133023.
33. Ruan Y, Guo Y, Kowal P, et al. Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China. *BMC Geriatr* 2019;19:327. https://doi.org/10.1186/s12877-019-1342-5; PMID: 31796000.
34. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39:412–23. https://doi.org/10.1093/ageing/afq034; PMID: 20392703.
35. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr* 2008;27:793–9. https://doi.org/10.1016/j.clnu.2008.06.013; PMID: 18718696.
36. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56. https://doi.org/10.1093/gerona/56.3.M146; PMID: 11253156.
37. Winograd CH, Gerety MB, 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.tb02700.x; PMID: 1906492.
38. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev* 2016;26:53–61. https://doi.org/10.1016/j.arr.2015.12.003; PMID: 26674984.
39. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. In search of an integral conceptual definition of frailty: opinions of experts. *J Am Med Dir Assoc* 2010;11:338–43. https://doi.org/10.1016/j.jamda.2009.09.015; PMID: 20511101.
40. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci* 2006;61:262–6. https://doi.org/10.1093/gerona/61.3.262; PMID: 16567375.
41. Yang X, Lupón J, Vidán MT, et al. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. *J Am Heart Assoc* 2018;7:e008251. https://doi.org/10.1161/JAHA.117.008251; PMID: 30571603.
42. Vermeiren S, Vella-Azzopardi R, Beckwée D, et al. frailty and the prediction of negative health outcomes: A meta-analysis. *J Am Med Dir Assoc* 2016;17:1163.e1–17. https://doi.org/10.1016/j.jamda.2016.09.010; PMID: 27886869.
43. 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.
44. Vitale C, Jankowska E, Hill L, et al. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;21:1299–305. https://doi.org/10.1002/ejhf.1611; PMID: 31646718.
45. 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.
46. Izawa KP, Watanabe S, Osada N, et al. Handgrip strength as a predictor of prognosis in Japanese patients with congestive heart failure. *Eur J Cardiovasc Prev Rehabil* 2009;16:21–7. https://doi.org/10.1097/HJR.0b013e32831269a3; PMID: 19237993.
47. Pavasini R, Serenelli M, Celis-Morales CA, et al. Grip strength predicts cardiac adverse events in patients with cardiac disorders: an individual patient pooled meta-analysis. *Heart* 2019;105:834–41. https://doi.org/10.1136/heartjnl-2018-313816; PMID: 30455175.
48. Fuentes-Abolafio IJ, Stubbs B, Pérez-Belmonte LM, et al. Physical functional performance and prognosis in patients with heart failure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2020;20:512. https://doi.org/10.1186/s12872-020-01725-5; PMID: 33297975.
49. Chaudhry SI, McAvay G, Chen S, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;61:635–42. https://doi.org/10.1016/j.jacc.2012.11.027; PMID: 23391194.
50. Pulignano G, Del Sindaco D, Di Lenarda A, et al. Incremental value of gait speed in predicting prognosis of older adults with heart failure: insights from the IMAGE-HF Study. *JACC Heart Fail* 2016;4:289–98. https://doi.org/10.1016/j.jchf.2015.12.017; PMID: 26970831.
51. Hornsby WE, Sareini MA, Golbus JR, et al. Lower extremity function is independently associated with hospitalization burden in heart failure with preserved ejection fraction. *J Card Fail* 2019;25:2–9. https://doi.org/10.1016/j.cardfail.2018.09.002; PMID: 30219550.
52. Perez-Moreno AC, Jhund PS, Macdonald MR, et al. Fatigue as a predictor of outcome in patients with heart failure: analysis of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail* 2014;2:187–97. https://doi.org/10.1016/j.jchf.2014.01.001; PMID: 24720928.
53. Vogels RL, Scheltens P, Schroeder-Tanka JM, et al. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9:440–9. https://doi.org/10.1016/j.ejheart.2006.11.001; PMID: 17174152.
54. Sokoreli I, Pauws SC, Steyerberg EW, et al. 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.
55. Boxer R, Kleppinger A, Ahmad A, et al. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail* 2010;16:208–13. https://doi.org/10.1111/j.1751-7133.2010.00151.x; PMID: 20887617.
56. Madan SA, Fida N, Barman P, et al. Frailty assessment in advanced heart failure. *J Card Fail* 2016;22:840–4. https://doi.org/10.1016/j.cardfail.2016.02.003; PMID: 26883168.
57. McNallan SM, Chamberlain AM, Gerber Y, et al. Measuring frailty in heart failure: a community perspective. *Am Heart J* 2013;166:768–74. https://doi.org/10.1016/j.ahj.2013.07.008; PMID: 24093859.
58. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33. https://doi.org/10.1097/00005650-199603000-00003; PMID: 8628042.
59. Tanaka S, Kamiya K, Hamazaki N, et al. Incremental value of objective frailty assessment to predict mortality in elderly patients hospitalized for heart failure. *J Card Fail* 2018;24:723–32. https://doi.org/10.1016/j.cardfail.2018.06.006; PMID: 30010026.
60. Jha SR, Hannu MK, Chang S, et al. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. *Transplantation* 2016;100:429–36. https://doi.org/10.1097/TP.0000000000000991; PMID: 26516676.
61. Dominguez-Rodriguez A, Abreu-Gonzalez P, Jimenez-Sosa A, et al. The impact of frailty in older patients with non-ischaemic cardiomyopathy after implantation of cardiac resynchronization therapy defibrillator. *Europace* 2015;17:598–602. https://doi.org/10.1093/europace/euu333; PMID: 25564552.
62. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes

after implantation of left ventricular assist device as destination therapy. *J Heart Lung Transplant* 2014;33:359–65. https://doi.org/10.1016/j.healun.2013.12.014; PMID: 24486165.
63. Chung CJ, Wu C, Jones M, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. *J Card Fail* 2014;20:310–5. https://doi.org/10.1016/j.cardfail.2014.02.008; PMID: 24569037.
64. Heberton GA, Nassif M, Bierhals A, et al. Usefulness of psoas muscle area determined by computed tomography to predict mortality or prolonged length of hospital stay in patients undergoing left ventricular assist device implantation. *Am J Cardiol* 2016;118:1363–67. https://doi.org/10.1016/j.amjcard.2016.07.061; PMID: 27622708.
65. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726. https://doi.org/10.1093/eurheartj.ehab368; PMID: 34447992.
66. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439–50. https://doi.org/10.1001/jama.2009.454; PMID: 19351941.
67. Palmer K, Bowles KA, Paton M, et al. Chronic heart failure and exercise rehabilitation: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 2018;99:2570–82. https://doi.org/10.1016/j.apmr.2018.03.015; PMID: 29698639.
68. Piepoli MF, Davos C, Francis DP, et al. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189. https://doi.org/10.1136/bmj.37938.645220.EE; PMID: 14729656.
69. Taylor RS, Walker S, Smart NA, et al. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol* 2019;73:1430–43. https://doi.org/10.1016/j.jacc.2018.12.072; PMID: 30922474.
70. Taylor RS, Long L, Mordi IR, et al. Exercise-based rehabilitation for heart failure: Cochrane systematic review, meta-analysis, and trial sequential analysis. *JACC Heart Fail* 2019;7:691–705. https://doi.org/10.1016/j.jchf.2019.04.023; PMID: 31302050.
71. Gomes Neto M, Durães AR, Conceição LSR, et al. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. *Int J Cardiol* 2018;261:134–41. https://doi.org/10.1016/j.ijcard.2018.02.076; PMID: 29572084.
72. Adamopoulos S, Parissis J, Karatzas D, et al. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. *J Am Coll Cardiol* 2002;39:653–63. https://doi.org/10.1016/S0735-1097(01)01795-8; PMID: 11849865.
73. Conraads VM, Beckers P, Bosmans J, et al. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J* 2002;23:1854–60. https://doi.org/10.1053/euhj.2002.3239; PMID: 12445534.
74. Pullen PR, Nagamia SH, Mehta PK, et al. Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure. *J Card Fail* 2008;14:407–13. https://doi.org/10.1016/j.cardfail.2007.12.007; PMID: 18514933.
75. Sciatti E, Lombardi C, Ravera A, et al. Nutritional deficiency in patients with heart failure. *Nutrients* 2016;8:422. https://doi.org/10.3390/nu8070442; PMID: 27455314.
76. Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur Heart J* 2017;38:2279–86. https://doi.org/10.1093/eurheartj/ehx235; PMID: 28498942.
77. Keith M, Quach S, Ahmed M, Azizi-Namini P, et al. Thiamin supplementation does not improve left ventricular ejection fraction in ambulatory heart failure patients: a randomized controlled trial. *Am J Clin Nutr* 2019;110:1287–95. https://doi.org/10.1093/ajcn/nqz192; PMID: 31504093.
78. Herrmann M, Stanger O, Paulweber B, et al. Effect of folate supplementation on N-terminal pro-brain natriuretic peptide. *Int J Cardiol* 2007;118:267–9. https://doi.org/10.1016/j.ijcard.2006.07.034; PMID: 17052779.
79. Witte KK, Nikitin NP, Parker AC, et al. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. *Eur Heart J* 2005;26:2238–44. https://doi.org/10.1093/eurheartj/ehi442; PMID: 16081469.
80. McKeag NA, McKinley MC, Harbinson MT, et al. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: a randomized, placebo-controlled trial. *JACC Heart Fail* 2014;2:308–17. https://doi.org/10.1016/j.jchf.2013.12.008; PMID: 24952700.
81. Rozentryt P, von Haehling S, Lainscak M, et al. The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. *J Cachexia Sarcopenia Muscle* 2010;1:35–42. https://doi.org/10.1007/s13539-010-0008-0; PMID: 21475692.
82. Aquilani R, Opasich C, Gualco A, et al. Adequate energy-protein intake is not enough to improve nutritional and metabolic status in muscle-depleted patients with chronic heart failure. *Eur J Heart Fail* 2008;10:1127–35. https://doi.org/10.1016/j.ejheart.2008.09.002; PMID: 18835539.
83. Pineda-Juárez JA, Sánchez-Ortiz NA, Castillo-Martínez L, et al. Changes in body composition in heart failure patients after a resistance exercise program and branched chain amino acid supplementation. *Clin Nutr* 2016;35:41–7. https://doi.org/10.1016/j.clnu.2015.02.004; PMID: 25726428.
84. Bonilla-Palomas JL, Gámez-López AL, Castillo-Domínguez JC, et al. Nutritional intervention in malnourished hospitalized patients with heart failure. *Arch Med Res* 2016;47:535–40. https://doi.org/10.1016/j.arcmed.2016.11.005; PMID: 28262195.
85. Essa H, Oguguo E, Douglas H, et al. One year outcomes of heart failure multispecialty multidisciplinary team virtual meetings. *Eur Heart J* 2021;42:(Suppl 1):971. https://doi.org/10.1093/eurheartj/ehab724.0971.
86. Gill TM, Baker DI, Gottschalk M, et al. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med* 2002;347:1068–74. https://doi.org/10.1056/NEJMoa020423; PMID: 12362007.
87. 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.
88. Rockwood K, Stadnyk K, 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.
89. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc* 2001;49:1691–9. https://doi.org/10.1046/j.1532-5415.2001.49281.x; PMID: 11844005.
90. Abellan van Kan G, Rolland YM, Morley JE, et al. 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.